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# Health and Environmental Effects Profile for Phenol

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# HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR PHENOL

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16. ABSTRACT

The Health and Environmental Effects Profile for Phenol was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. Phenol has been determined to be a systemic toxicant. A Reference Dose (RfD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime, for phenol is 0.04 mg/kg/day for oral exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for phenol is 10.

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## PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through July, 1984. This document was finalized in June, 1985. However, a subsequent re-evaluation of the original data cited resulted in this revised draft as of February, 1987.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of $q_1^*$ is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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TABLE OF CONTENTS


| | | Page |
|---|---|---|
| 1. | INTRODUCTION | 1 |
| 1.1. | STRUCTURE AND CAS NUMBER | 1 |
| 1.2. | PHYSICAL AND CHEMICAL PROPERTIES | 1 |
| 1.3. | PRODUCTION DATA | 2 |
| 1.4. | USE DATA | 4 |
| 2. | ENVIRONMENTAL FATE AND TRANSPORT PROCESSES | 5 |
| 2.1. | AIR | 5 |
| 2.2. | WATER | 7 |
| 2.3. | SOIL | 11 |
| 3. | EXPOSURE | 13 |
| 3.1. | AIR | 13 |
| 3.2. | WATER | 15 |
| 3.3. | FOOD | 16 |
| 3.4. | DERMAL | 17 |
| 4. | PHARMACOKINETICS | 18 |
| 4.1. | ABSORPTION | 18 |
| 4.2. | DISTRIBUTION | 20 |
| 4.3. | METABOLISM | 23 |
| 4.4. | EXCRETION | 34 |
| 5. | EFFECTS | 39 |
| 5.1. | CARCINOGENICITY | 39 |
| 5.2. | MUTAGENICITY | 43 |
| 5.3. | TERATOGENICITY | 46 |
| 5.4. | OTHER REPRODUCTIVE EFFECTS | 49 |
| 5.5. | SUBCHRONIC AND CHRONIC TOXICITY | 49 |
| 5.6. | OTHER RELEVANT INFORMATION | 58 |
| 6. | AQUATIC TOXICITY | 61 |
| 6.1. | ACUTE TOXICITY | 61 |
| 6.2. | CHRONIC EFFECTS | 63 |
| 6.3. | PLANT EFFECTS | 63 |
| 6.4. | RESIDUE | 64 |
| 6.5. | OTHER RELEVANT INFORMATION | 64 |

TABLE OF CONTENTS (cont.)


| | Page |
|---|---|
| 7. EXISTING GUIDELINES AND STANDARDS | 65 |
| 7.1. HUMAN | 65 |
| 7.2. AQUATIC | 65 |
| 8. RISK ASSESSMENT | 66 |
| 9. REPORTABLE QUANTITIES RANKING (RQ) | 73 |
| 9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY | 73 |
| 9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY | 79 |
| 10. REFERENCES | 80 |
| APPENDIX: LITERATURE SEARCHED | 109 |

## LIST OF TABLES


| No. | Title | Page |
|---|---|---|
| 1-1 | Phenol Production | 3 |
| 3-1 | Atmospheric Phenol Concentration in Various Sites in the United States | 14 |
| 4-1 | Distribution of Phenol in Rabbits That Died or Were Killed Within 6 Hours after an Oral Dose of 0.5 g of Phenol/kg bw. | 24 |
| 4-2 | Tissue Distribution of Phenol and its Metabolites in *N. alexis*. | 26 |
| 4-3 | Urinary Metabolites of Phenol in Various Species. | 29 |
| 5-1 | Animal; Agent: Phenol | 40 |
| 5-2 | Genotoxicity Testing of Phenol. | 44 |
| 5-3 | Subchronic and Chronic Oral Toxicity of Phenol. | 50 |
| 5-3 | Symptom Distribution of Cases of Human Ingestion of Phenol and Controls | 53 |
| 5-5 | Subchronic Inhalation Toxicity of Phenol. | 56 |
| 9-1 | Composite Scores for Phenol | 76 |
| 9-2 | Phenol: Minimum Effective Dose (MED) and Reportable Quantity (RQ) | 78 |

## LIST OF FIGURES


| No. | Title | Page |
|---|---|---|
| 4-1 | Tissue Distribution of Phenol and its Metabolites at Various Time Intervals After One-Half Oral $LD_{50}$ Dose of Phenol. . . . . | 21 |
| 4-2 | Metabolism of Phenol in a Rabbit given a Lethal Oral Dose (0.5 g/kg) of Phenol. . . . . | 27 |
| 4-3 | Metabolism of Phenol in a Rabbit given a Sublethal Oral Dose (0.3 g/kg) of Phenol . . . . . | 28 |
| 4-4 | Concentrations and Excretion of Phenol in Urine in a Subject Exposed to Phenol Vapor in a Concentration of 18.3 $mg/m^3$ by Inhalation. . . . . | 36 |
| 4-5 | Excretion of Phenol in Urine of a Subject Exposed to a Concentration of 24.4 $mg/m^3$ for 6 hours with Absorption Through the Skin. . . . . | 37 |
| 4-6 | Excretion Rate of 'Excess' Phenol as a Function of Time of Exposure and, After its Termination, Expressed as a Fraction Of Absorption Rate. . . . . | 38 |

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADI | Acceptable daily intake |
| BCF | Bioconcentration factor |
| bw | Body weight |
| CAS | Chemical Abstract Service |
| CS | Composite score |
| DMBA | 9,10-dimethyl-1,2-benzanthracene |
| DMSO | Dimethyl sulfoxide |
| DNA | Deoxyribonucleic acid |
| $EC_{50}$ | Median effective concentration |
| $K_{oc}$ | Soil sorption coefficient standardized with respect to organic carbon |
| $K_{om}$ | Sorption coefficient standardized with respect to soil organic matter |
| $K_{ow}$ | Octanol/water partition coefficient |
| $LC_{50}$ | Concentration lethal to 50% of recipients (and all other subscripted dosage levels) |
| $LD_{50}$ | Dose lethal to 50% of recipients |
| LOAEL | Lowest-observed-adverse-effect level |
| MATC | Maximum acceptable toxicant concentration |
| MED | Minimum effective dose |
| NOAEL | No-observed-adverse-effect level |
| NOEL | No-observed-effect level |
| ppb | Parts per billion |
| ppm | Parts per million |
| ppt | Parts per trillion |
| RfD | Reference dose |
| RQ | Reportable quantity |

## LIST OF ABBREVIATIONS (cont.)

| | |
|---|---|
| $RV_d$ | Dose-rating value |
| $RV_e$ | Effect-rating value |
| SCE | Sister chromatid exchange |
| SGOT | Serum glutamic oxaloacetic transaminase |
| TLV | Threshold limit value |
| TWA | Time-weighted average |
| UF | Uncertainty factor |
| v/v | Volume per volume |
| w/v | Weight per volume |

# 1. INTRODUCTION

## 1.1. STRUCTURE AND CAS NUMBER

Phenol is a substituted benzene compound with one hydroxyl group attached to the benzene ring. It was first isolated from coal tar in 1834 and was named carbolic acid (Thurman, 1982). Some of its other synonyms are hydroxybenzene, phenic acid and phenylic acid (Verschueren, 1983). The structure of phenol is given below:

Empirical formula: $C_6H_6O$

Molecular weight : 94.11

The CAS registry number for this compound is 108-95-2.

## 1.2. PHYSICAL AND CHEMICAL PROPERTIES

In the pure form, phenol is a white crystalline solid with a characteristic odor. It tends to turn brown-black in color upon exposure to air and light (Thurman, 1982; Windholz, 1983). Some of the physical properties of phenol are given below:

| | | |
|---|---|---|
| Melting point: | 40.9°C | Thurman (1982) |
| Boiling point at 1 atmosphere: | 181.8°C | Thurman (1982) |
| $pK_a$ at 25°C (acid dissociation constant): | 9.9 | Thurman (1982) |
| Vapor pressure at 25°C: | 0.341 mm of Hg | Mabey et al. (1981) |
| Specific gravity: | 1.07 | Verschueren (1983) |

| | | |
|---|---|---|
| Solubility in water at 25°C: | 93,000 mg/ℓ | Callahan et al. (1979) |
| log $K_{ow}$: | 1.46 | Verschueren (1983) |
| $K_{oc}$: | 16.2-91 | Briggs (1981); Boyd (1982); Scott et al. (1983) |
| Conversion factor at 20°C: | 1 ppm ~3.92 mg/m³ | Verschueren (1983) |

The $K_{oc}$ values given above were estimated using the equation, $K_{oc} = 1.724\ K_{Om}$ (Lyman et al., 1982).

Phenol reacts with strong bases, forming salts that ionize into phenate and the corresponding cation. (Thurman, 1982). Phenol also undergoes substitution reaction (Thurman, 1982). The halogenated substitution reaction products of phenol are significant because they may be formed during the chlorination of potable water. The chlorophenols formed impart an offensive odor to drinking water (Wajon et al., 1982). When $ClO_2$ was used as a disinfectant ($ClO_2$/phenol molar ration >3), however, no chlorination product was detected (Wajon et al., 1982). Similarly, phenol and its objectionable reaction products can be removed from water through ozonation (Singer and Gurol, 1983; Gould and Weber, 1976).

Phenol also undergoes various condensation reactions, which are commercially important for the manufacture of phenolic resins (Thurman, 1982).

## 1.3. PRODUCTION DATA

The most widely used processes for phenol production are cumene hydroperoxidation and toluene oxidation (Thurman, 1982). Details of these two processes and other less used processes have been given by Thurman (1982). Table 1-1 lists the companies that produce phenol in the United States as of January, 1984.

TABLE 1-1

Phenol Production*

| Manufacturer | Annual Capacity (millions of pounds) |
|---|---|
| Allied Corp., Frankford, PA | 500 |
| Clark Chem. Corp., Blue Island, IL | 88 |
| Diamond-Shamrock Corp., Tuscaloosa, AL | 10 |
| Dow Chem., Oyster Creek, TX | 465 |
| Ferro Corp., Santa Fe Springs, CA | 8 |
| General Electric Co., Mount Vernon, IN | 400 |
| Georgia-Pacific Corp., Bound Brook, NJ | 157 |
| Plaquemin, NJ | 330 |
| Getty-oil Co., El Dorado, KS | 95 |
| Kalama Chem., Inc., Kalama, WA | 75 |
| Koppers Co., Inc., Follansbee, WV | 8 |
| Merichem Co., Houston, TX | 20 |
| Shell Oil Co., Deer Park, TX | 500 |
| Stimson Lumber Co., Anacortes, WA | 2 |
| U.S. Steel Corp., Haverhill, OH | 520 |
| TOTAL | 3178 |

*Source: SRI, 1984

Monsanto Company stopped production of phenol at its Alvin, TX facility in 1984 decreasing the production capacity of phenol by 500 million pounds from its 1983 production capacity (Anonymous, 1984). Excluding production from coke ovens and gas retort ovens, the 1983 production volume for phenol was 2.64 billion pounds (USITC, 1984).

## 1.4. USE DATA

The consumption pattern of phenol in the United States in recent years is as follows: phenolic resins, 45%; bisphenol A, 20%; caprolactam, 13%; alkyl phenols, 5%; cresols and xylenols, 5%; aniline, 3%; miscellaneous usage, 5%; and export, 4% (CMR, 1984).

## 2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

### 2.1. AIR

The primary sources of atmospheric phenol emission as a result of its manufacturing processes are vents from storage tanks and transport loading (Delaney and Hughes, 1979). If a total emission factor of 0.161 pounds/$10^3$ pounds is assumed for these two sources (Delaney and Hughes, 1979), the total atmospheric emission of phenol from the manufacture of 2.64 billion pounds is estimated to be ~0.4 million pounds/year.

The atmospheric fate of phenol has not been studied comprehensively. An experimental value for the rate constant of hydroxyl radical reaction with phenol is not available. Based on a correlation equation, $\log K = -11.578 - 2.120\Sigma_p$ (where $\Sigma_p = -0.36$) for the rate constant K for addition of OH to substituted benzenes (Hendry and Kenley, 1979), the rate constant for OH reaction with phenol is estimated as $1.51 \times 10^{-11}$ $cm^3$ $molecule^{-1}$ $sec^{-1}$. On the basis of this rate constant and the concentration of OH radical in the atmosphere at $10^6$ molecules $cm^{-3}$, the half-life of phenol in the atmosphere that is due to OH reaction is estimated to be ~0.5 day. This atmospheric half-life of phenol can also be estimated by considering that the reactivity of phenol towards OH radical reaction is ~3.8 times faster than OH radical reaction toward propane (Sickles et al., 1980), and the half-life for propane reaction with OH radicals is 3.6 days (Hendry and Kenley, 1979). Therefore, the half-life for phenol reaction with OH radicals is estimated to be <1 day.

The rate constant for ozone reaction with phenol is estimated to be 1 to $2 \times 10^{-18}$ $cm^3$ $molecule^{-1}$ $sec^{-1}$ (Hendry and Kenley, 1979). Assuming the atmospheric concentration of $O_3$ as $10^{12}$ molecule $cm^{-3}$ (Lyman et al., 1982), the half-life of phenol that is due to ozone reaction is estimated to be 4-8 days.

The rate constant for nitrate radical ($NO_3\cdot$) reaction with phenol has been estimated to be $2\times10^{-12}$ $cm^3$ $mole^{-1}$ $sec^{-1}$ (Carter et al., 1981). Nitrate radicals are formed in photochemical smog systems from the reaction of $O_3$ with $NO_2$: $O_3 + NO_2 \rightarrow NO_3 + O_2$. In fact, during an air pollution episode in the Los Angeles basin, up to 355 ppt ($8.9\times10^9$ molecule $cm^{-3}$) of $NO_3$ was detected ~1 hour after sunset (Carter et al., 1981). Under these conditions, the half-life of phenol because of its reaction with $NO_3$ radical is <1 minute. Therefore, in polluted atmospheres where relatively high concentration of $O_3$ and $NO_2$ may be present, the fate of phenol may be determined by its reaction with $NO_3$ radicals.

The possibility of phenol photooxidation in air was explored by Knoevenagel and Himmelreich (1976). When phenol vapor in humid air was irradiated with a high pressure mercury lamp at 50°C, ~11% degradation of phenol was observed in 24 hours. Assuming a first order decay, this corresponds to a half-life of ~14 days; however, this experiment used a higher temperature and light of shorter wavelength than would be available under ambient atmospheric conditions. Consequently, the estimated half-life is a significant underestimate of the actual photolytic half-life of phenol in ambient air. The investigation of Knoevenagel and Himmelreich (1976) demonstrates, however, the possibility of photoreaction of phenol in the atmosphere. Callahan et al. (1979) also considered the possibility of phenol photoreaction in the atmosphere.

The rate of physical removal processes for phenol from the atmosphere were not reported in the available literature cited in the Appendix. Based on a report by Cupitt (1980), it can be speculated that significant removal of phenol from the air through adsorption on aerosol particles or dry depo-

sition is not likely. The solubility of phenol in water is high enough to permit significant removal of this chemical from air through wet deposition.

In summary, in a polluted atmosphere that contains $NO_x$ at a concentration $\geq$20 ppb (Carter et al., 1981), phenol will be removed from the atmosphere with a half-life of <1 hour through its reaction with $NO_3$ radicals. In the absence of a significant $NO_x$ concentration, phenol will be removed from the atmosphere with a half-life of ~0.5 day through its reaction with OH radicals. Some phenol is likely to be removed through wet precipitation, although no quantitative value for this removal rate can be given.

## 2.2. WATER

The two sources of phenol occurring naturally in aquatic media are animal wastes and decomposition of organic wastes (U.S. EPA, 1981). The anthropogenic sources of phenol are coal tar (Thurman, 1982) and wastewater from manufacturing industries such as resins, plastics, fibers, adhesives, iron and steel, aluminum, leather and rubber (U.S. EPA, 1981). Effluents from synthetic fuel manufacturing processes are also anthropogenic sources of phenol (Parkhurst et al., 1979).

The data regarding the fate of phenol in aquatic media are relatively more abundant. The three most likely chemical processes of phenol in aquatic media are its interaction with peroxy radicals ($RO_2\cdot$), hydroxyl radicals ($OH\cdot$) and singlet oxygen ($^1O_2$). The rate constants for these three respective reactions are $10^7$ $M^{-1}$ $hr^{-1}$, $3.24\times10^{12}$ $M^{-1}$ $hr^{-1}$, and $<7\times10^9$ $M^{-1}$ $hr^{-1}$ (Mabey et al., 1981; Neta and Schuler, 1975). If the concentrations of $RO_2\cdot$, $OH\cdot$ and $^1O_2$ in natural aquatic media are assumed to be $10^{-9}$, $10^{-17}$ and $10^{-12}$ M, respectively (Mill et al.,

1980), the only significant reaction in aquatic media will be phenol reaction with peroxy radicals. The half-life for this reaction is estimated to be ~3 days. The autooxidation of phenol by $OH^-$ ions at pH 7 was studied by Moussavi (1979); the half-life for this process was estimated to be ~26 days.

The direct photolysis of phenol in aquatic media is probably not environmentally significant (Mabey et al., 1981). Recently, Draper and Crosby (1983) irradiated 1 µmol/ℓ of phenol in water in July sunlight in Davis, CA, and failed to detect any expected oxidation products; however, the significance of photodegradation of phenol in natural waters in the presence of likely photosensitizers has not been studied (Dufek et al., 1982; Callahan et al., 1979).

The available data indicate that biodegradation in aquatic media is the primary fate-determining process for phenol. Several authors have shown that isolated microorganisms can biodegrade phenol rather quickly. Some of these microorganisms include strains of Pseudomonas putida, Trichosporon cutaneum, Alcaligenes eutrophus, Bacillus stearothermophilus and Candida tropicalis (Gaal and Neujahr, 1979; Hughes et al., 1984; Hill and Robinson, 1975; Bayly and Wigmore, 1973; Yang and Humphrey, 1975; Feist and Hegeman, 1969; Buswell, 1975; Janke et al., 1981; Paris et al., 1982). Strains of Pseudomonas putida represent the most frequently studied microorganisms used in determining the biodegradation potential of phenol. Phenol is microbially oxidized to catechol by this microorganism (Paris et al., 1982). It has been estimated that the microbial transformation rate constant for phenol with Pseudomonas putida is $7 \times 10^{-12}$ ℓ $cell^{-1}$ $hr^{-1}$ (Paris et al., 1982)

The degradation of phenol with a mixed culture of microorganisms has also been studied. With both activated sludge and settled domestic wastewater as microbial inoculum, phenol has been shown to degrade rather rapidly (Kincannon et al., 1983; Pitter, 1976; Petrasek et al., 1983; Davis et al., 1981; Bridie et al., 1979a; Beltrame et al., 1979; 1980; Tabak et al., 1981). For example, using settled domestic wastewater as microbial inoculum, Tabak et al. (1981) observed rapid adaptation of the microorganisms to achieve optimum biodegradation rates for phenol. At a phenol concentration in the range of 5-10 mg/ℓ, 95-97% of phenol biodegraded in 7 days with the original culture. The biodegradation rate was 100% in 7 days with adapted microorganisms (Tabak et al., 1981).

Although the above studies for the microbial degradation of phenol with isolated and mixed microorganisms indicate the likelihood of biodegradation of phenol in natural aquatic media, these studies cannot be used to derive the half-life of phenol due to biodegradation in natural bodies of water. The biodegradation rate constant for phenol in natural pond and river water is estimated to be $3.3 \times 10^{-10}$ ℓ $cell^{-1}$ $hr^{-1}$ (Paris et al., 1983). If the concentration of microorganisms in freshwater is assumed to be $10^{8}$ cell $\ell^{-1}$ (Banerjee et al., 1984), the half-life of phenol in freshwater is <1 day. Rubin and Alexander (1983) have shown that organic and inorganic nutrients in natural waters affect the rate of biodegradation of phenol. Thus the degradation rate in freshwater is likely to be different from estuarine water. The half-life for degradation of phenol in estuarine water is estimated to be 9 days (Lee and Ryan, 1979). The biodegradation of aquatic phenol under anaerobic conditions was studied by Healy and Young (1979) and by Boyd et al. (1983). The adaptation period under anaerobic conditions is usually longer (Healy and Young, 1979) and the biodegradation

rate slower (Boyd et al., 1983) than for aerobic biodegradation. A complete anaerobic biodegradation time of 2 weeks has been reported for phenol (Boyd et al., 1983).

Significant removal of phenol from aquatic media by evaporation is not likely (Aaberg et al., 1983). Studies in Dow laboratories showed that no phenol evaporated from dilute aqueous solution after aeration of the solution for 4 hours (Federal Register, 1979). The biological treatment of wastewater containing phenol has also shown that <1% of phenol is removed by stripping (Kincannon et al., 1983; Petrasek et al., 1983).

Although Issaacson and Frink (1984) estimated a much higher sorption coefficient value for the sorption of phenol onto wet sediment compared with the value reported by many investigators for air-dried soils (see Section 1.1.), the studies of Aaberg et al. (1983) and Kincannon et al. (1983) show that sorption of phenol onto sediment in aquatic media is undoubtedly of minor importance compared with biodegradation under most circumstances.

Since potable water is subjected to chlorination or ozonation, it is important to determine the fate of phenol under these treatment processes. The oxidation of phenol by $O_3$ and $ClO_2$ used during the water treatment process can be rapid. If aqueous chlorine is used as a disinfectant, it imparts an objectionable odor from the formation of chlorophenols in phenol-containing water, unless a large excess of chlorine is applied (Wajon et al., 1982). The disinfectant $ClO_2$, however, does not form chlorinated products as long as the $ClO_2$/phenol molar ratio is >3 (Wajon et al., 1982). Phenol can be oxidized within 2 seconds at pH 7 by $ClO_2$ (Wajon et al., 1982). Similarly, the reaction of phenol with $O_3$ in aqueous solution was studied by several investigators and was found to be pH-dependent, with higher pH enhancing the decomposition rate of phenol (Singer and Gurol,

1983; Gould and Weber, 1976). The half-life of phenol oxidation (phenol concentration of up to 140 mg/ℓ) by ozone (concentration of 7 mg/ℓ) at pH 6-9 was estimated to be <10 minutes (Singer and Gurol, 1983).

Available data indicate that phenol does not bioconcentrate in edible aquatic organisms. From the $K_{ow}$ data, Branson (1978) estimated a log BCF value of 0.9 in the muscle of rainbow trout. The investigations of Kobayashi et al. (1979) and Aaberg et al. (1983) drew the same conclusion. For example, in a static exposure experiment, Kobayashi et al. (1979) estimated a log BCF value of 0.30 in goldfish whole body. The investigation of Call et al. (1980), however, indicates that the metabolites of phenol are rapidly taken up by fish.

## 2.3. SOIL

Pertinent data regarding the possible chemical reactions of phenol in soil were not found in the available literature. Based on its photolytic behavior in aquatic media, it is unlikely that phenol will undergo significant photolysis in soil. Available data indicate that phenol will biodegrade under both aerobic and anaerobic soil conditions. For example, Baker and Mayfield (1980) observed 100% degradation of phenol in 5 days in a clay loam soil under aerobic conditions, compared with 15% degradation in 40 days with sterile control. Under anerobic conditions, 20% phenol degraded in 40 days compared with 7% degradation in 40 days in sterile control (Baker and Mayfield, 1980). Qualitative evidence of anaerobic degradation of phenol in ground water has also been provided (Ehrlich et al., 1982). Rizet et al. (1977) reported 100% degradation of phenol in soil in 5 days. In a soil percolation study, Walker (1954) reported 100% degradation of phenol in 2 days following a 2-day lag time. These studies all indicate that biodegradation of phenol in soil will be rapid and will be its fate determining process.

The estimated soil $K_{oc}$ range of 16.2-91 (see Section 1.2.) for phenol suggests that it will not be sorbed significantly to soil. Ehrlich et al. (1982) observed very little sorption of phenol on aquifer sediments. Despite its high water solubility and poor sorption to soil, biodegradation will be sufficiently rapid so that the probability of groundwater contamination will be low (Ehrlich et al., 1982), except in cases of spills or leaching from landfill sites. In these cases, high concentrations of phenol may destroy degradating microbial populations leading to groundwater contamination (Ehrlich et al., 1982; Delfino and Dube, 1976). Although no experimental data are available, judging from its volatility from aquatic media it can be speculated that the evaporation of phenol from soil surfaces will not be significant in cases other than spills.

## 3. EXPOSURE

### 3.1. AIR

Reliable atmospheric phenol monitoring data from eight sites in the United States are available (Brodzinsky and Singh, 1982). The measured phenol concentration in each site, the type of site, and the median concentration of phenol near source areas are given in Table 3-1.

Using data from Table 3-1 it appears that the median concentration of phenol in the only non-point source urban/suburban area monitored is ~120 ng/m³. In source-dominated areas, the median phenol concentration is ~20,000 ng/m³. During a smog episode in West Covina, CA in July, 1973, Cronn et al. (1977) measured the concentrations of several pollutants in the air particulate matter. The concentration of phenol ranged from 60-350 ng/m³, with a mean concentration of 200 ng/m³. [The vast majority of phenol is expected to be present in the gas/vapor phase rather than sorbed onto air particulate matter (see Section 2.1.)]. The atmospheric phenol concentration in Osaka City, Japan, in 1979 averaged ~3000 ng/m³ (Kuwata et al., 1980).

The atmospheric concentrations of phenol in the occupational areas are expected to be higher. In a casting factory in Osaka City, Japan, the atmospheric concentration of phenol was measured at ~2 mg/m³ (Kuwata et al., 1980). The atmospheric concentration of phenol in Bakelite factories in Japan was reported to be as high as 12.5 mg/m³ (Ohtsuji and Ikeda, 1972). A phenol concentration of ~4000 ng/m³ was reported in the ambient air near a fishmeal factory in Japan (Hoshika et al., 1981). Kuwata et al. (1980) reported an average concentration of 1.1 mg/m³ of phenol in auto exhaust and an average of 347 µg of phenol in the smoke from each Japanese

TABLE 3-1

Atmospheric Phenol Concentration in Various Sites in the United States*

| Site | Site Type | Sampling Date | No of Sampling Points | Median Conc. (ppt) |
|---|---|---|---|---|
| Columbus, OH | urban/suburban | 1974 | 7 | 30 |
| Edison, NJ | source area | 1976 | 9 | 520 |
| El Dorado, AR | source area | 1978 | 10 | 10,000 |
| El Paso, TX | source area | 1978 | 22 | 44,000 |
| Elizabeth, NJ | source area | 1978 | 17 | 1,300 |
| Houston, TX | source area | 1977 | 10 | 990 |
| Kansas City, MO | source area | 1974 | 1 | 7,800 |
| Upland, CA | source area | 1977 | 14 | 1,400 |
| MEDIAN OF ALL REPLICATE SAMPLES FROM SOURCE AREAS | | | | 5,000 |

*Source: Brodzinsky and Singh, 1982

cigarette. Hoffmann et al. (1975), however, reported 139 and 77 µg phenol in the mainstream smoke of United States tobacco and marijuana cigarettes, respectively.

## 3.2. WATER

Phenol has been monitored in surface water, in treated and untreated effluent from industrial discharges, and in groundwater from landfill sites, coal gasification sites, and accidental spill sites. During the National Organic Monitoring Survey, phenol was qualitatively detected in 2 of 110 raw water supplies analyzed (U.S. EPA, 1980). The annual mean concentration of phenol in the lower Mississippi River water was reported to be 1.5 µg/ℓ (U.S. EPA, 1980). The concentration of phenol in water from Lake Huron, Detroit River and St. Clair River collected during the period 1972-77 was reported to range from not detected to 24 µg/ℓ (Konasewich et al., 1978). Phenol was reported to be present (not quantified) in a Niagara River watershed (Elder et al., 1981). The river water in an unspecified location in the United States was reported to contain 10-100 µg/ℓ of phenol (Jungclaus et al., 1978). Sheldon and Hiles (1979) reported up to 0.3 µg/ℓ of phenol in Delaware River water near Philadelphia, PA. Phenol was detected (not quantified) in Glatt River in Switzerland (Zuercher and Giger, 1976). The Oba Dan Lake in Nigeria was reported to contain ~850 µg/ℓ of phenol (Osibanjo and Ajayi, 1980). The concentration of phenol in Hayashida River water in Japan was reported to be 895 µg/ℓ (Yasuhara et al., 1981).

Phenol was detected in several wastewater samples. The primary and secondary effluent samples of Los Angeles City Treatment Plant were reported to contain 32 and <10 µg/ℓ of phenol, respectively (Young et al., 1983).

The separator effluent from a petroleum refinery wastewater contained a maximum of 33.5 mg/ℓ of phenol (Pfeffer, 1979). Parkhurst et al. (1979) reported the concentrations of phenol in treated and untreated effluent from a coal conversion plant at 4 and 4780 mg/ℓ, respectively. The maximum concentration of phenol in shale oil wastewater was reported to be 4.5 mg/ℓ (Hawthorne and Sievers, 1984).

Phenol was also reported to be present in several groundwater samples. The maximum phenol concentration in groundwater near two underground coal gasification sites was reported to be 10.2 mg/ℓ (Stuermer et al., 1982). Phenol at a maximum concentration of 1.9 mg/ℓ was reported in several leachates from landfill sites in Illinois (Clark and Piskin, 1977; Sawhney and Kozloski, 1984). Phenol was detected (not quantified) in the leachate from dumpsites in Australia (Stepan et al., 1981). After an accidental spill of phenol in southeastern Wisconsin in July, 1974, phenol was detected in well water in several homes for a period of at least 1.5 years after the incident (Delfino and Dube, 1976; Baker et al., 1978). The maximum concentration of phenol in one well was reported to be 1130 mg/ℓ.

### 3.3. FOOD

There are no surveys of phenol levels in foods that will allow an estimate of the daily dietary intake. Phenol has been reported at a concentration of 7 and 28.6 mg/kg in smoked summer sausage and smoked pork belly (U.S. EPA, 1980). Medical preparations including ointments, ear drops, cold sore lotions, mouthwashes, gargles, toothache drops, analgesic rubs and nose drops contain phenol (Douglas, 1972). A commercial antiseptic lotion was reported to contain 1.4% phenol (Musto et al., 1977). Chloraseptic lozenges have been reported to contain 32.5 mg of total phenol (free phenol and sodium phenolates) per lozenge (U.S. EPA, 1980) and Kaiser (1967) reported the presence of phenol in black fermented tea.

## 3.4. DERMAL

Besides occupational exposure, a number of medicinal products for skin applications, feminine hygiene products and hemorrhoidal products can be sources of dermal exposure to phenol (U.S. EPA, 1980). No estimate for dermal exposure to phenol, however, was found in the available literature.

# 4. PHARMACOKINETICS

## 4.1. ABSORPTION

Phenol is readily absorbed by oral, inhalation and dermal routes of exposure (Deichmann and Keplinger, 1981). Oral absorption can be presumed from the known oral toxicity of phenol in humans (Brancato, 1982) and experimental animals (Section 5).

Humphrey et al. (1980), in an *in situ* absorption study in which the small intestine of Sprague-Dawley rats was isolated and $^{14}C$-phenol (40 mg/kg) was introduced, found that the disappearance of added phenol from the intestinal lumen seemed to follow first-order kinetics. The half-life of $^{14}C$ in the intestinal lumen was 5.5±0.5 minutes, and the rate constant for intestinal absorption of $^{14}C$ was 0.127±0.003 $min^{-1}$.

In an experiment designed to examine the distribution of $^{14}C$-phenol administered by gavage to male Sprague-Dawley rats, Liao and Oehme (1981) found 28.4% of the administered dose in the tissues at 0.5 hour.

Ohtsuji and Ikeda (1972) collected urine samples from workmen who were exposed to phenol vapors in closed workrooms for 7 hours/day. The total urinary phenol concentration and the urinary conjugated phenol concentration varied in proportion to the environmental phenol concentration, while the concentration of unconjugated phenol in urine was independent of the environmental phenol concentrations. When estimated values for the amount of phenol inhaled per hour were compared with estimates for the amount of phenol excreted per hour, these authors concluded that phenol was readily absorbed in the human lung.

In an experiment performed on human volunteers, subjects inhaled phenol in air at concentrations ranging from 6-20 $mg/m^3$ through a face mask for an exposure period of 8 hours with two 0.5-hour breaks (Piotrowski, 1971).

The concentrations of phenol were determined by analyzing the urine collected from subjects before, during and after the exposure. The concentrations of phenol were also determined in the inhaled and expired air every hour. Subjects retained from 60-88% of the phenol to which they were exposed.

Hogg et al. (1981) studied the uptake of $^{14}$C-phenol by excised trachea-lung preparations from male hooded rats. When an aqueous solution of $^{14}$C-phenol was introduced through a tracheal cannula and the entire trachea-lung preparation was immersed in isotonic saline for 3 hours, the amount of radioactivity transferred to the saline was 53% (range 34-70%) of the original amount injected. When isolated rat lungs were perfused with heparinized whole blood, the maximal level of radioactivity in the perfusate was reached 25 minutes after the intratracheal administration of $^{14}$C-phenol. When perfusion was stopped (after 2-3 hours), 92% of the radioactivity was in the perfusate, 3% was associated with lung tissue, and 6% was recovered by lung lavage.

Because of its medicinal uses as a topical anesthetic and disinfectant and because of accidental spills in industrial situations resulting in skin contact, the most important route of human exposure to phenol and the best characterized with respect to absorption is the dermal route. Piotrowski (1971) also exposed human volunteers (naked or clothed) to three different concentrations of phenol in the air (5, 10 and 25 mg/m$^3$) for a 6-hour period. Fresh air was supplied for breathing to preclude any absorption of phenol through the lungs. Urine was collected before, during and after exposure and analyzed for phenol. The absorption rate of phenol vapor through the skin was found to be proportional to the concentration of the phenol vapor. The investigator calculated a mean absorption coefficient of

0.35 $m^3$/hr, that is, the subjects absorbed through the skin per hour the amount of phenol contained in 0.35 $m^3$ of air. No protective effect of clothing could be discerned.

Skin absorption *in vivo* in 12 human volunteers was studied by Baranowska-Dutkiewicz (1981). Phenol in aqueous solution (2.5, 5.0 or 10.0 g/ℓ) was applied to a 15.9 $cm^2$ area of the forearm skin (held in place by a watch glass) and allowed to remain for 15, 30 or 60 minutes. At the end of the exposure period, the remaining phenol was washed from the skin and the watch glass. The absorbed dose was calculated as the difference between the amount originally applied to the skin and the amount recovered by washing after exposure. The amount of phenol absorbed was dependent on both concentration and exposure time. The rate of absorption was also dependent on concentration. At a concentration of 2.5 g/ℓ, the absorption rate ranged from 0.079($\pm$0.026)-0.098($\pm$0.029) mg/$cm^2$/hour; at 5.0 g/ℓ the absorption rate was 0.181($\pm$0.047) mg/$cm^2$/hour; at 10.0 g/ℓ the absorption rate was 0.301($\pm$0.048) mg/$cm^2$/hour.

Sixteen infants with seborrhoeic eczema, ranging in age from 2-5 months, were painted in the diaper area twice daily over a 48-hour period with Magenta Paint B.P.C., which contains 4.0 g phenol in a total volume of 100 mℓ (Rogers et al., 1978). An average of 32 mℓ of paint covering ~11-15% of the body surface was applied to each child. Phenol was detected in the urine of four babies.

## 4.2. DISTRIBUTION

Uniformly labeled $^{14}C$-phenol (207 mg/kg bw) was administered by gavage to male Sprague-Dawley rats weighing 400-500 g (Liao and Oehme, 1981). Animals were killed at stated intervals (from 0.5-16 hours after dosing) and the radioactivity in a number of tissues was determined (Figure 4-1). At

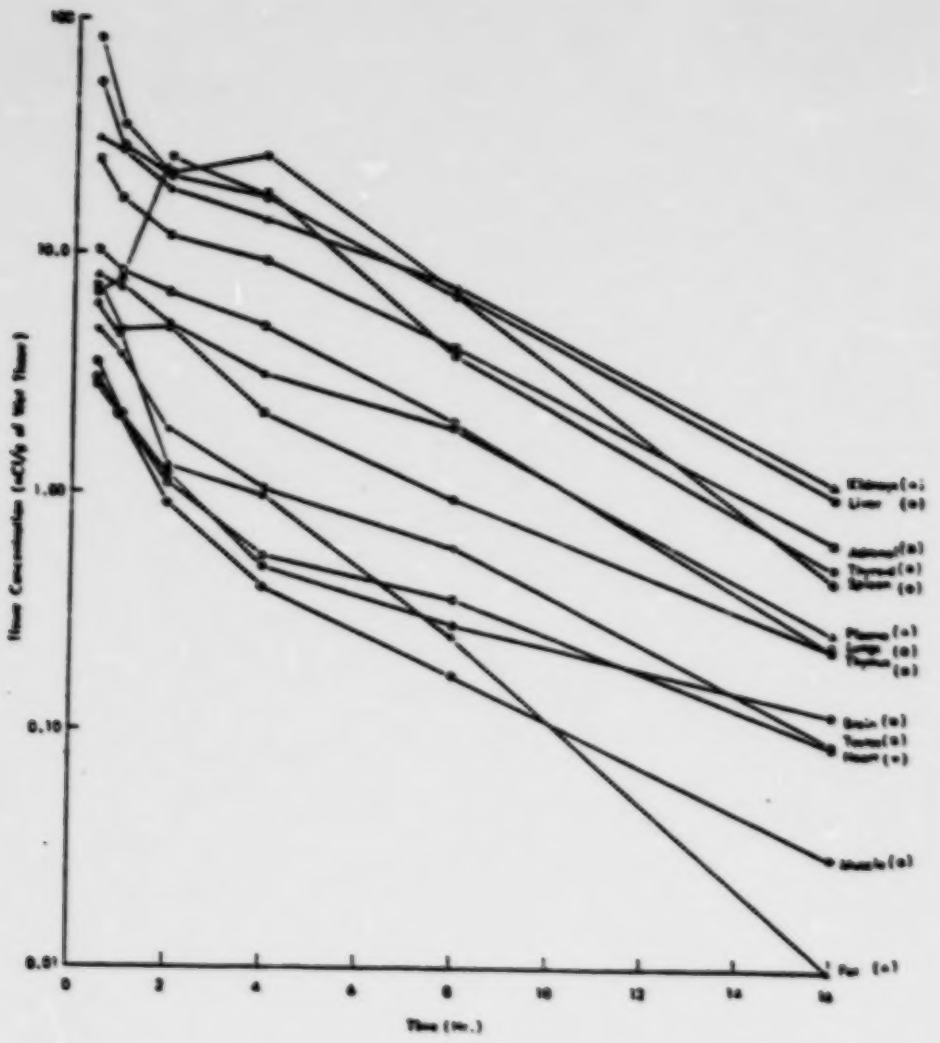


FIGURE 4-1

Tissue distribution of phenol and its metabolites at various time intervals after one-half oral $LD_{50}$ dose of phenol. Due to the complexity of the figure, standard errors were not shown.

Source: Liao and Oehme, 1981

0.5 hours, 28.4% of the administered dose was found in the tissues. Four tissues, liver, kidney, spleen and adrenal gland, had phenol concentrations greater than the concentration in plasma at all times studied. Liver contained an average of 42% (range 29-56%) of the total radioactivity recovered from the body. Approximately 67.0-85.1% of the radioactivity found in blood was present in the plasma fraction and, of that, 41.0-49.6% was bound to plasma proteins or other macromolecules.

The plasma disappearance of radioactive label was studied when $^{14}C$-phenol was injected i.v. into dogs, cats, pigs and goats (Oehme, 1969). Plasma disappearance was most rapid in goats and slowest in cats. Tissue binding of phenol was indicated in all species, but the cat, by the calculation of apparent volumes of distribution of phenol of >100%. The plasma protein binding of phenol was ~60% in all species.

The kinetics of phenol disappearance from the blood of laboratory mice, Mus musculus and Australian desert rodents, Notomys alexis, were characterized by Wheldrake et al. (1978). The half-life of the disappearance of i.p. injected $^{14}C$-phenol from the blood of M. musculus was 12.9 minutes at a dose level of 5 mg/kg and 13.9 minutes at 100 mg/kg. In N. alexis, the half-life was 14.1 minutes at 5 mg/kg and 19.4 minutes at 100 mg/kg. At the lower dose level, the circulating halflife of phenol was similar in both species, but at the higher dose, phenol was cleared faster in M. musculus.

Deichmann (1944) administered 500 mg phenol/kg bw to five rabbits and killed them by air embolism when twitching first began (within 1-3 minutes of dosing). Elevated quantities of phenol were found in all the tissues studied. Liver (20.9-30.4 mg phenol/100 g tissue weight), lungs (5.1-17.1 mg/100 g), blood (6.2-12.6 mg/100 g), brain and spinal cord (3.1-10.4 mg/100 g) and kidneys (2.3-7.1 mg/100 g) contained the most phenol. Another

group of five rabbits was dosed similarly, but the time of death after administration of phenol ranged from 15 minutes to 6 hours. The results of the tissue and media analysis are presented in Table 4-1. Within 15 minutes of administration of phenol, the highest concentrations were found in the liver, kidneys, lungs, brain and spinal cord, and blood. As time progressed, tissue concentrations of phenol decreased, except in the kidney, where concentrations remained relatively constant over the 6-hour period studied.

$^{14}$C-phenol was injected i.p. into four groups of N. alexis (6 animals/group) (Wheldrake et al., 1978). The animals were killed by cervical dislocation, and tissue samples were analyzed for radioactivity. The results are presented in Table 4-2. At the time of the peak plasma phenol level (30 minutes after dosing), kidney and lung showed the highest phenol concentrations at both dose levels.

## 4.3. METABOLISM

Phenol is a natural component of animal and human tissues; however, tissue levels of phenol can be elevated upon exposure to exogenous sources of phenol or chemicals that are metabolized to phenol such as benzene or phenylsalicylate (Babich and Davis, 1981). The metabolism of exogenous phenol has been presented most clearly by Deichmann and Keplinger (1981). The fate of phenol when administered as a lethal oral dose and a sublethal oral dose to rabbits is depicted in Figures 4-2 and 4-3, respectively.

The four metabolites of phenol reported most frequently are phenyl sulfate, phenyl glucuronide, quinol sulfate (1,4-benzenediolsulfate) and quinol glucuronide; however, their importance is relative to species and dose level (Table 4-3). After oral administration of $^{14}$C-phenol to 19 species, Capel et al. (1972 a,b) collected urine for 24 hours. Radiochroma-

TABLE 4-1

Distribution of Phenol in Rabbits That Died or Were Killed within 6 Hours after an Oral Dose of 0.5 g of Phenol/kg bw[a]

| Tissue or Media | Phenol | Died After 15 Minutes | Died After 82 Minutes | Killed After 2 Hours | Killed After 2.5 Hours | Killed After 6 Hours |
|---|---|---|---|---|---|---|
| | | Concentration of Phenol in mg/100 g of Tissue | | | | |
| Liver | free | 63.7 | 22.4 | 3.4 | 13.5 | 0.5 |
| | conjugated | 0.9 | 4.2 | 3.2 | 6.0 | 9.4 |
| | total[b] | 64.6 | 26.6 | 6.6 | 19.5 | 9.9 |
| Blood | free | 30.8 | 22.4 | 5.8 | 11.3 | 6.5 |
| | conjugated | 0.9 | 5.3 | 8.0 | 10.2 | 9.8 |
| | total[b] | 31.7 | 27.7 | 13.8 | 21.5 | 16.3 |
| Kidneys | free | 35.3 | 13.4 | 4.8 | 11.2 | 2.6 |
| | conjugated | 0.8 | 7.4 | 22.8 | 12.9 | 30.0 |
| | total[b] | 36.1 | 20.8 | 27.6 | 24.1 | 32.6 |
| Lungs | free | 34.2 | 20.8 | 5.4 | 12.2 | 1.5 |
| | conjugated | 1.8 | 4.7 | 6.7 | 5.1 | 3.0 |
| | total[b] | 36.0 | 25.5 | 12.1 | 17.3 | 4.5 |
| Heart, thymus, testes, spleen | free | 53.0 | 21.0 | 6.8 | 14.0 | 7.5 |
| | conjugated | 0.6 | 2.3 | 5.7 | 5.1 | 7.7 |
| | total[b] | 53.6 | 23.3 | 12.5 | 19.1 | 15.2 |
| Brain and cord | free | 31.3 | NR | 6.8 | 10.4 | 2.5 |
| | conjugated | 0.5 | NR | 0.7 | 0.3 | 0.4 |
| | total[b] | 31.8 | NR | 7.5 | 10.7 | 2.9 |

TABLE 4-1 (cont.)

| Tissue or Media | Phenol | Died After 15 Minutes | Died After 82 Minutes | Killed After 2 Hours | Killed After 2.5 Hours | Killed After 6 Hours |
|---|---|---|---|---|---|---|
| | | Concentration of Phenol in mg/100 g of Tissue | | | | |
| Muscle | free | 19.0 | 8.2 | 9.2 | 12.0 | 10.1 |
| | conjugated | 0 | 0.5 | 1.1 | 0.8 | 1.4 |
| | total[b] | 19.0 | 8.7 | 10.3 | 12.8 | 11.5 |
| Urine | free | NR | 0.5 | NR | 11.6 | 11.0 |
| | conjugated | no sample | 14.0 | no sample | 52.0 | 12.3 |
| | total[b] | NR | 14.5 | NR | 63.6 | 23.3 |
| Exhaled air | free | 0 | 0.1[c] | 0.7[c] | 0.1[c] | 0.2[c] |
| | conjugated | NR | NR | NR | NR | NR |
| | total[b] | 0 | 0.1 | 0.7 | 0.1 | 0.2 |

[a]Source: Deichmann, 1944

[b]Total phenol obtained by summation of free and conjugated fractions

[c]Phenol in total air exhaled

NR = Not reported

TABLE 4-2

Tissue Distribution of Phenol and its Metabolites in N. alexis[a,b]

| | Dose | | | |
|---|---|---|---|---|
| | 5 mg/kg | | 100 mg/kg | |
| Tissue | 30 Minutes | 120 Minutes | 30 Minutes | 120 Minutes |
| Blood | 1.000 | 1.000 | 1.000 | 1.000 |
| Liver | 0.300±0.027 | 0.898±0.116 | 0.579±0.113 | 1.409±0.459 |
| Kidney | 1.555±0.209 | 1.393±0.074 | 3.188±0.198 | 1.936±0.268 |
| Heart | 0.312±0.040 | 0.772±0.101 | 0.518±0.040 | 0.640±0.143 |
| Skeletal muscle | 0.197±0.027 | 0.628±0.050 | 0.210±0.013 | 0.726±0.132 |
| Brain | 0.076±0.016 | 0.593±0.089 | 0.190±0.014 | 0.304±0.057 |
| Lung | 0.682±0.030 | 1.700±0.346 | 0.894±0.036 | 1.292±0.251 |
| Spleen | 0.447±0.070 | 2.062±0.178 | 0.554±0.096 | 1.707±0.541 |

[a]Source: Wheldrake et al., 1978

[b]Concentrations are normalized against blood = 1.000

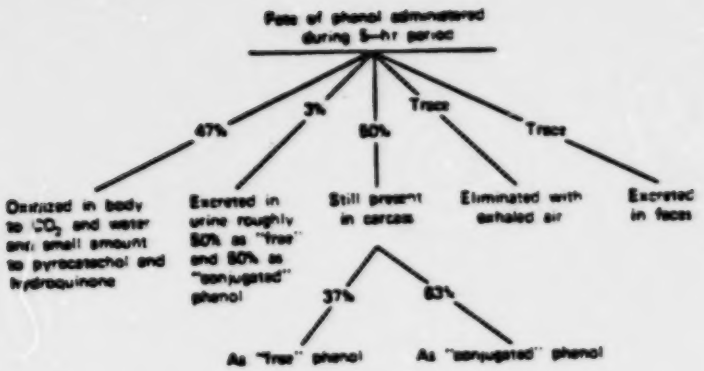


FIGURE 4-2

Metabolism of Phenol in a Rabbit Given
a Lethal Dose (0.5 g/kg) of Phenol

Source: Deichmann and Keplinger, 1981

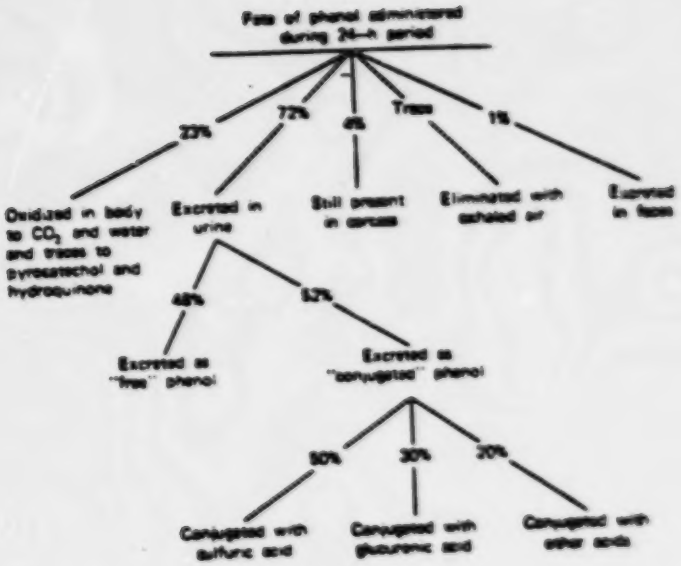


FIGURE 4-3

Metabolism of Phenol in a Rabbit Given a Sublethal Oral Dose (0.3 g/kg) of Phenol

Source: Deichmann and Keplinger, 1981

TABLE 4-3

Urinary Metabolites of Phenol in Various Species

| Species | Dose (mg/kg)/ Route | % Dose Excreted in 24 hours | % Excreted in 24 hours found as: Phenyl Sulfate | Quinol Sulfate | Phenyl Glucuronide | Quinol Glucuronide | Total Sulfate | Total Glucuronide | Total Quinol | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| **Primates** | | | | | | | | | | |
| Man (3M) | 0.01/oral | 90 | 77 | 1[a] | 16 | tr | 78 | 16 | 1 | Capel et al., 1972a |
| Rhesus monkey (2F) | 50/oral | 43 | 65 | ND | 35 | ND | 65 | 35 | ND | Capel et al., 1972a |
| Rhesus monkey (1M, 1F) | 0.01/i.m. | 83 | NR | NR | NR | NR | 95 | 5 | NR | Mehta et al., 1978 |
| Rhesus monkey (1M, 1F) | 1/i.m. | 66 | NR | NR | NR | NR | 93 | 7 | NR | Mehta et al., 1978 |
| Rhesus monkey (1M, 1F) | 10/i.m. | 80 | NR | NR | NR | NR | 78 | 22 | NR | Mehta et al., 1978 |
| Rhesus monkey (1M, 1F) | 25/i.m. | 68 | NR | NR | NR | NR | 63 | 37 | NR | Mehta et al., 1978 |
| Squirrel monkey (3F) | 25/oral | 31 | 7 | ND | 68 | 25 | 7 | 93 | 25 | Capel et al., 1972a |
| Cynomolgus monkey (1F) | 0.01/i.m. | 69 | NR | NR | NR | NR | 95 | 5 | NR | Mehta et al., 1978 |
| Cynomolgus monkey (1F) | 1/i.m. | 70 | NR | NR | NR | NR | 92 | 8 | NR | Mehta et al., 1978 |
| Cynomolgus monkey (1F) | 10/i.m. | 98 | NR | NR | NR | NR | 67 | 33 | NR | Mehta et al., 1978 |
| Cynomolgus monkey (1F) | 25/i.m. | 64 | NR | NR | NR | NR | 54 | 46 | NR | Mehta et al., 1978 |
| Capuchin (1F) | 25/oral | 73 | 14 | ND | 65 | 21 | 14 | 86 | 21 | Capel et al., 1972a |
| Capuchin (2F) | 0.01/i.m. | 30 | NR | NR | NR | NR | 71 | 29 | NR | Mehta et al., 1978 |
| Capuchin (2F) | 1/i.m. | 39 | NR | NR | NR | NR | 55 | 45 | NR | Mehta et al., 1978 |
| Capuchin (2F) | 10/i.m. | 39 | NR | NR | NR | NR | 40 | 60 | NR | Mehta et al., 1978 |
| Capuchin (2F) | 25/oral | 40 | NR | NR | NR | NR | 21 | 79 | NR | Mehta et al., 1978 |
| Tamarin (1M) | 10/i.m. | 93 | NR | NR | NR | NR | 11 | 89 | NR | Mehta et al., 1978 |
| Bushbaby (1)[b] | 10/i.m. | 60 | NR | NR | NR | NR | 76 | 24 | NR | Mehta et al., 1978 |
| Tree shrew (1)[b] | 10/i.m. | 61 | NR | NR | NR | NR | 52 | 48 | NR | Mehta et al., 1978 |
| **Carnivores** | | | | | | | | | | |
| Ferret (3F)[c] | 25/oral | 51 | 28 | 30 | 40 | ND | 58 | 40 | 30 | Capel et al., 1972a |
| Cat (3F)[c] | 25/oral | 59 | 87 | 13 | ND | ND | 100 | ND | 13 | Capel et al., 1972a |
| Cat (1M; 1F) | 20/i.v. | 68[d] | 80 | 20 | ND | ND | 100 | ND | 20 | Miller et al., 1976 |
| Cat (1M, 1F) | 40/i.v. | 73[d] | 78 | 16 | ND | ND | 94[e] | ND | 20 | Miller et al., 1976 |
| Dog (1M, 1F)[c] | 25/oral | 58 | 50 | 32 | 18 | ND | 82 | 18 | 32 | Capel et al., 1972a |

TABLE 4-3 (cont.)

| Species | Dose (mg/kg)/ Route | % Dose Excreted in 24 hours | % Excreted in 24 hours found as: Phenyl Sulfate | Quinol Sulfate | Phenyl Glucuronide | Quinol Glucuronide | Total Sulfate | Total Glucuronide | Total Quinol | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| **Rodents** | | | | | | | | | | |
| Rat (3F; Wistar) | 25/oral | 95 | 54 | 1 | 42 | 2 | 55 | 44 | 3 | Capel et al., 1972a |
| Rat (4NR; Wistar) | 25/oral | 97 | 55[f] | 1[f] | 42[f] | 2[f] | 56[f] | 44[f] | 3[f] | Kao et al., 1979 |
| Mouse (30[g]F; ICI) | 25/oral | 66 | 46 | 5 | 35 | 15 | 51 | 50 | 20 | Capel et al., 1972a |
| Jerboa (3F; Egytian) | 25/oral | 47 | 61 | 12 | 26 | 1 | 73 | 27 | 13 | Capel et al., 1972a |
| Gerbil (2F; 1M) | 25/oral | 55 | 42 | 19 | 35 | 1 | 61 | 36 | 20 | Capel et al., 1972a |
| Hamster (2F; golden) | 25/oral | 76 | 26 | 1 | 43 | 28 | 27 | 71 | 29 | Capel et al., 1972a |
| Lemming (3F; steppe) | 25/oral | 40 | 35 | 10 | 39 | 15 | 45 | 54 | 25 | Capel et al., 1972a |
| Guinea pig (2F; English) | 25/oral | 64 | 18 | tr | 78 | 5 | 18 | 83 | 5 | Capel et al., 1972a |
| **Miscellaneous** | | | | | | | | | | |
| Pig (3F; large White) | 21/oral | 51 | ND | ND | 100 | ND | ND | 100 | ND | Capel et al., 1972a |
| Pig (2[b]; large White) | 25/oral | 86 | 1[fa] | tr[fa] | 86[f] | 7[f] | 1[fa] | 93[f] | 7[f] | Kao et al., 1979 |
| Sheep (2M) | 25/oral | 87 | 33[f] | 4[f] | 48[f] | 4[f] | 37[f] | 52[f] | 9[fh] | Kao et al., 1979 |
| Hedgehog (2M; European) | 20/oral | 39 | 75 | 10 | 15 | ND | 85 | 15 | 10 | Capel et al., 1972a |
| Fruitbat (2F; Indian) | 25/oral | 54 | 10 | ND | 90 | ND | 10 | 90 | ND | Capel et al., 1972a |
| Rabbit (3F; New Zealand White) | 25/oral | 48 | 45 | 9 | 46 | ND | 54 | 46 | 9 | Capel et al., 1972a |
| Chicken (3F; Rhode Island Red) | 25/oral | 57 | 78 | ND | 22 | ND | 78 | 22 | ND | Capel et al., 1972a |

[a] one subject only

[b] sex not known

[c] mongrel

[d] % dose excreted in 6 hours

[e] 4% of the dose excreted as unconjugated quinol; 2% excreted as unconjugated phenol

[f] % excreted in 8 hours found as the indicated metabolite

[g] Three determinations were made with the urine of 10 mice pooled for each determination.

[h] Phenyl phosphate (11%) and quinol phosphate (1%) were also found as metabolites of phenol in this species.

i.m. = Intramuscular; i.v. = intravenous; M = male; F = female; tr = <1% of urinary $^{14}C$; ND = not detected; NR = not reported

tograms of the urine showed that 8 of the species studied excreted all 4 metabolites; 6 species excreted 3 metabolites; 4 species excreted 2; and 1 species excreted only 1. Virtually no sulfate conjugate was found in the pig urine. These results in the pig were confirmed by Kao et al. (1979).

Kao et al. (1979) administered $^{14}$C-phenol by gavage to sheep, pigs and rats (see Table 4-3). In addition to the four metabolites detected in most other species, sheep were found to produce a significant amount (~12% of the total recovered radioactivity) of phenyl and quinol phosphate.

As reported by Capel et al. (1972a), cats did not produce glucuronide conjugates of phenol or its metabolite, quinol (see Table 4-3). At an i.v. dose of 20 mg $^{14}$C-phenol/kg bw, 80% of the radioactivity recovered from the urine within 6 hours was present as phenyl sulfate and 20% as quinol sulfate (Miller et al., 1976). At 40 mg $^{14}$C-phenol/kg bw, 6% of the radioactivity recovered in the urine was unconjugated phenol (2%) or quinol (4%), indicating that the sulfate conjugation mechanism was saturated at this dose level.

*In vitro* studies of phenol conjugation in liver preparations from *N. alexis* demonstrated that at low phenol concentrations, the formation of phenyl sulfate predominated over the formation of phenyl glucuronide (Ramli and Wheldrake, 1981). As phenol concentrations increased, the ratio of phenyl glucuronide to phenyl sulfate also increased. This increase in glucuronide formation, relative to sulfate formation, has been observed in this species *in vivo* (Wheldrake et al., 1978) and also in rhesus, cynomolgus and capuchin monkeys (Mehta et al., 1978) (see Table 4-3).

Ramli and Wheldrake (1981) suggested that the preferential formation of phenyl sulfate over phenyl glucuronide at low dose levels in *N. alexis* is due to the higher affinity of sulfotransferase ($K_m$=1.9x10$^{-5}$ M) for

phenol compared with glucuronyl transferase ($K_m$=6.4x10$^{-4}$ M). The *in vitro* studies also demonstrate that the slow rate of formation of the sulfate donating co-substrate of the reaction, 3'-phosphoadenosine-5'-phosphosulfate (PAPS), becomes the rate-limiting step at high phenol concentrations.

Koster et al. (1981), in a similar investigation of the dose-dependence glucuronidation:sulfation ratio in male Wistar rats *in vivo* or isolated hepatocytes *in vitro*, found that the likeliest explanation for the shift in the ratio is the saturation of the sulfotransferase at a lower dose than the glucuronyl transferase, rather than the depletion of inorganic sulfate. The results of Weitering et al. (1979), regarding the incorporation of $^{35}$S-sulfate into phenyl sulfate in male Wistar rats, support the data of Koster et al. (1981).

When $^{14}$C-phenol was introduced into excised rat trachea-lung preparations, Hogg et al. (1981) found that the amount of conjugated phenol was dependent on the amount of phenol added to the system. The amount of conjugated phenol found after a 3-hour incubation at 37°C, when 27.2 µg of phenol was added, was 83.2%; when the dose was 272 µg, 73.1% was conjugated; when the dose was 2.72 mg, 65.1% was conjugated. Phenyl sulfate and phenyl glucuronide were present in almost equal amounts at each dose level. Quinol sulfate was detected, in some experiments, as a minor metabolite. When isolated rat lungs were perfused with whole blood for 2-3 hours, only 15% of the radioactivity detected in plasma samples was present as unconjugated phenol.

Whole body autoradiography of young rats given $^{14}$C-phenol either orally or i.p. indicated that the level of isotope in areas corresponding to the liver did not, at any time, exceed blood isotope levels, leading the

authors to suggest that the liver is not the principal site of phenol detoxication (Powell et al., 1974). In further experiments with isolated, perfused segments of rat small intestine, all of the added $^{14}$C-phenol was conjugated after a 2-hour incubation period; 95% was present as phenyl glucuronide and 5% as phenyl sulfate. When rat gut segments were perfused in situ, the radioactivity which appeared in the portal blood was associated with $^{14}$C-phenol conjugates. No free $^{14}$C-phenol was detected. Powell et al. (1974) suggested that the intestinal tract is the major site of detoxication of orally administered phenol.

In support of the observations of Powell et al. (1974), Cassidy and Houston (1980a) found that only 3% of orally administered phenol (1.5 mg/kg in male Sprague-Dawley rats) entered the systemic circulation as unconjugated phenol. The main determinate of phenol detoxication was the intestinal enzymes, which conjugated 92% of the total dose. The hepatic enzymes conjugated ~6% (0.48% of the administered dose) of the remaining unconjugated phenol reaching the liver. Pulmonary enzymes conjugated 62% (4.66% of the administered dose) of the free phenol reaching the lungs.

In another experiment designed to distinguish between systemic biotransformation (presumed to occur primarily in the liver) and biotransformation occurring in a single pass across the lung, Cassidy and Houston (1980b) injected $^{14}$C-phenol into male Sprague-Dawley rats. When administered into the left jugular vein, phenol must cross the lung before reaching the general systemic circulation; when administered into the left carotid artery, it is immediately available for tissue distribution. The authors found that ~60% of the administered phenol was conjugated by the lung on the first pass following i.v. administration. The pulmonary first pass was linear at low doses (0.4-1.5 mg/kg) but became saturated at higher doses.

Only 0.5-14% of $^{14}$C-phenol injected into the duodenal lumen of anesthetized male Sprague-Dawley rats reached the systemic circulation unconjugated by either the intestinal mucosa or the liver (which provided a minimal contribution) (Cassidy and Houston, 1980c). Following pulmonary first pass metabolism ($^{14}$C-phenol was administered through the left jugular vein), only 40-76% of the dose reached the systemic circulation unchanged. Based on the analysis of their data, the authors stated that the enzyme systems involved in these first pass effects are easily saturable.

## 4.4. EXCRETION

Capel et al. (1972 a,b) found that the recovery of labeled compounds in the 24-hour urine of 19 species dosed orally with $^{14}$C-phenol ranged from high (95%) for the rat to a low (31%) for the squirrel monkey, with the recovery for most species between 50 and 70%. Kao et al. (1979), in a study with sheep, pigs and rats, recovered 85, 84 and 90%, respectively, of the orally administered radioactivity within 3 hours of dosing; after 24 hours, the recovery was 87, 86 and 97%, respectively. Less than 0.5% of the administered radioactivity was recovered in the feces.

$^{14}$C-Phenol was administered i.v. to anesthetized cats, and urine and bile samples were collected at 1-hour intervals over 6 hours (Miller et al., 1976). At a dose of 20 mg/kg bw, 68% of the administered radioactivity was recovered from the urine within 6 hours. At 40 mg/kg bw, 73% of the radioactivity was recovered. None of the label administered to cats was detected in the bile after either dose (Miller et al., 1976). But when rat small intestines were perfused *in situ* with solutions containing $^{14}$C-phenol, 14.7$\pm$1.8% of the administered radioactivity was excreted in the bile within 1 hour (Humphrey et al., 1980).

In a study performed by Piotrowski (1971), human volunteers inhaled phenol vapor (6-20 mg/m³) over a period of 8 hours, with two 30-minute breaks. The excretion yield of phenol in the urine within 24 hours from the beginning of exposure was 99±8%. As depicted in Figure 4-4, the excretion rate rose rapidly during exposure, with the maximum value reached after exposure ended. The excretion rate then fell rapidly, approaching physiological levels within 24 hours. In the same study a similar pattern was seen when phenol vapor was absorbed through the skin rather than the lungs (Figure 4-5). No essential differences were seen in the kinetics of phenol excretion when dermal and inhalation exposure were compared. The kinetics of excretion best fit a one compartment model; however, as depicted in Figure 4-6, the theoretical curve deviates from the experimental data toward the end of the exposure period. Piotrowski (1971) suggested that more time is required for conjugation of phenol than can be predicted by the one-compartment model.

In a human study performed by Baranowski-Dutkiewicz (1981), 12 male volunteers each immersed one of their hands in an aqueous solution of phenol for 30 minutes. Maximum urinary excretion of phenol occurred between 3 and 5 hours after exposure. The results of this study differ only slightly from the results of Piotrowski (1971).

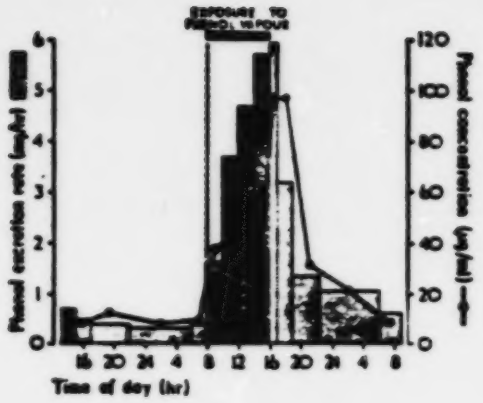


FIGURE 4-4

Concentrations and Excretion Rates of Phenol in Urine in a Subject Exposed to Phenol Vapor in a Concentration of 18.3 mg/m³ by Inhalation

Source: Piotrowski, 1971

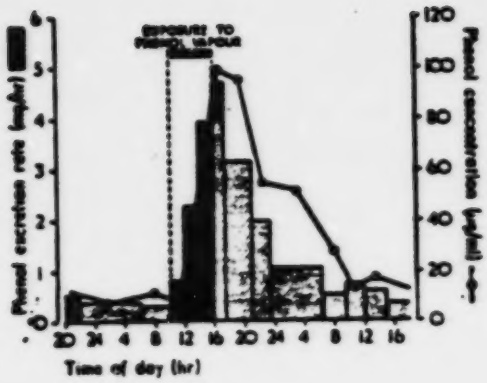


FIGURE 4-5

Excretion of Phenol in Urine of a Subject Exposed to a Concentration of 24.4 mg/m³ for 6 Hours with Absorption Through the Skin

Source: Piotrowski, 1971

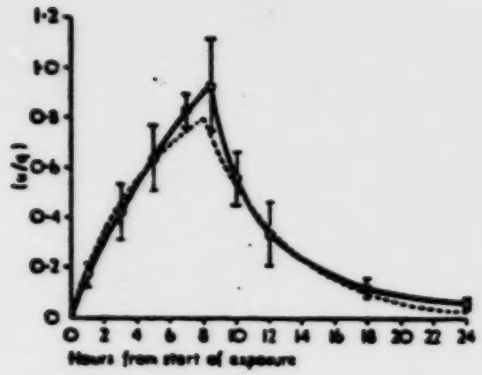


FIGURE 4-6

Excretion rate of "excess" phenol as a function of time of exposure and, after its termination, expressed as a fraction of absorption rate. (Mean values ± standard deviations. Line - theoretical curve for k=0.2 hour$^{-1}$.)

Source: Piotrowski, 1971

# 5. EFFECTS

## 5.1. CARCINOGENICITY

In an NCI (1980) bioassay, phenol was administered in the drinking water of F344 rats and B6C3F1 mice of both sexes at two concentrations (2500 and 5000 ppm) for 103 weeks. A dose-related decrease in weight gain, attributed to decreased water consumption, by treated animals was noted; no other clinical signs were observed. Survival was comparable among control and treated groups, with 44-60% of male rats, 74-78% of female rats and 80-96% of male and female mice surviving to the end of the study. Statistically significant incidences in pheochromocytomas of the adrenal medulla and leukemias or lymphomas were observed in low-dose male rats, compared with controls, and may have been associated with treatment; however, the incidences were not significantly different between high-dose males and the matched controls (Table 5-1). The incidence of C-cell carcinoma of the thyroid was significantly increased over control in low-dose male rats, but no differences were observed in the incidences of C-cell adenoma and C-cell adenoma or carcinoma. The increased incidence of interstitial cell tumors of the testis in low dose male rats was marginally significant. No increased incidences of tumors were observed in female rats or in male or female mice. This report concluded that, under the conditions of this bioassay, phenol was not carcinogenic for the animals employed; however, the primary reviewer of this report suggested that phenol be considered for retesting because of the equivocal results obtained in male rats.

Boutwell and Bosch (1959), studying on the ability of phenol to promote the formation of skin tumors in several strains of mice following a single dose of DMBA (initiator), found that phenol was not only positive as a tumor promoter but also as a weak complete carcinogen. Mice (23 females) from a

TABLE 5-1

Animal

Agent: Phenol[a]

| Exposure Route | Species/ Strain | Sex | Concentration (ppm) | Duration of Treatment (weeks) | Duration of Study (weeks) | Purity of Compound (%) | Vehicle | Target Organ | Tumor Type | Tumor Incidence (p value)[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| Oral | rat/ F344 | M | 0<br>2500<br>5000 | 103 | 105 | 98.47 | drinking water | hematopoietic system | monocytic leukemia | 18/50 (NS)<br>30/50 (p=0.014)<br>24/50 (NS) |
| Oral | rat/ F344 | M | 0<br>2500<br>5000 | 103 | 105 | 98.47 | drinking water | hematopoietic system | all leukemias | 18/50 (NS)<br>30/50 (p=0.014)<br>25/50 (NS) |
| Oral | rat/ F344 | M | 0<br>2500<br>5000 | 103 | 105 | 98.47 | drinking water | hematopoietic system | leukemia or lymphoma | 18/50 (NS)<br>31/50 (p=0.008)<br>25/50 (NS) |
| Oral | rat/ F344 | M | 0<br>2500<br>5000 | 103 | 105 | 98.47 | drinking water | adrenal | pheochromo-cytoma | 13/50 (NS)<br>22/50 (p=0.046)<br>9/50 (NS) |
| Oral | rat/ F344 | M | 0<br>2500<br>5000 | 103 | 105 | 98.47 | drinking water | thyroid | C-cell carcinoma | 0/50 (NS)<br>5/49 (p=0.027)<br>1/50 (NS) |
| Oral | rat/ F344 | M | 0<br>2500<br>5000 | 103 | 105 | 98.47 | drinking water | testis | interstitial cell tumor | 42/48 (NS)<br>49/50 (p=0.050)<br>47/50 (NS) |
| Oral | rat/ F344 | F | 0<br>2500<br>5000 | 103 | 105 | 98.47 | drinking water | No significant increased incidence of tumors in any tissue examined. | | |

TABLE 5-1 (cont.)

| Exposure Route | Species/ Strain | Sex | Concentration (ppm) | Duration of Treatment (weeks) | Duration of Study (weeks) | Purity of Compound (%) | Vehicle | Target Organ | Tumor Type | Tumor Incidence (p value)[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| Oral | mouse/ B6C3F1 | M | 0<br>2500<br>5000 | 103 | 105 | 98.47 | drinking water | No significant increased incidence of tumors in any tissue examined. | | |
| Oral | mouse/ B6C3F1 | F | 0<br>2500<br>5000 | 103 | 105 | 98.47 | drinking water | No significant increased incidence of tumors in any tissue examined. | | |

QUALITY OF EVIDENCE

Strengths of study: Adequate numbers of experimental and control animals of each sex were studied. Complete autopsies and histologic examinations were performed. Animals were exposed for a significant portion of their lifespan. Two species were studied at two exposure levels.

Weakness of study: The high spontaneous tumor rate noted for leukemias and lymphomas in male rats (36%, compared with the 15% historical incidence seen in other bioassays) was unexplained.

Overall adequacy: Adequate

Comments: The primary reviewer of this report recommended that phenol be considered for retesting because of the equivocal results obtained in male rats.

[a]Source: NCI, 1980

[b]The level of significance appearing beside incidences in the control group reflects the results of the Cochran-Armitage Test for Dose-related increase. The p values appearing beside the incidences in low-dose male rats reflect the results of Fisher's Exact Test.

NS = Not significant



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strain selectively bred for susceptibility to tumors induced by DMBA and croton oil were pretreated with a single dermal application of DMBA in benzene, to shaved skin (75 µg/animal). This procedure was followed after 1 week by a twice weekly application of 10% phenol in benzene (2.5 mg phenol/dose). A second group of animals (23 males) received DMBA alone with no secondary treatment, while a third group (24 females) received phenol alone with no pretreatment. The mice in the first group developed papillomas (95% of animals by week 13 of treatment) and carcinomas (73% of animals by week 42 of treatment) with a much greater incidence than animals in the second group (14% had papillomas at 42 weeks; no carcinomas) or the third group (36% had papillomas at 52 weeks; no carcinomas, one fibrosarcoma). Other strains of mice (Holtzman, CAF and C3H) treated with DMBA followed by phenol developed papillomas at a lower incidence than observed in the selectively bred mice treated with DMBA followed by phenol. The maximal tumor response was reached when 2.5 mg phenol/dose was applied. Fewer tumors developed when a dose of 1.25 mg (5% solution) was applied, while an application of 5.0 mg phenol (20% solution) caused death as a result of systemic toxicity.

Salaman and Glendenning (1957) found that phenol was a strong tumor promoter when a 20% solution was applied repeatedly to the skin of "S" strain albino mice, following initiation with 0.3 mg DMBA. This measure of phenol produced significant skin damage and was weakly carcinogenic when applied alone.

In a series of cocarcinogenicity studies in which 3 mg phenol was applied simultaneously with 5 µg benzo[a]pyrene, 3 times/week, to the backs of mice (female ICR/Ha Swiss), phenol partially inhibited benzo[a]pyrene carcinogenicity (Van Duuren and Goldschmidt, 1976; Van Duuren et al., 1971, 1973).

## 5.2. MUTAGENICITY

Phenol has been the subject of a variety of tests for mutagenicity, the results of which are summarized in Table 5-2. Phenol has been tested for mutagenicity in a number of bacterial test systems, with predominantly negative results. In a plate incorporation assay using histidine auxotrophs of Salmonella typhimurium, with and without S-9 mix from Aroclor-pretreated Sprague-Dawley rats, phenol concentrations ranging from 0.5-500 µg/plate did not produce reversions to histidine prototrophy (Pool and Lin, 1982). Florin et al. (1980), in similar tests using the same strains of S. typhimurium, also found that phenol did not exhibit any mutagenic activity. Haworth et al. (1983), using the same strains of S. typhimurium, also found negative results. Gocke et al. (1981), however, found that phenol showed mutagenic activity in S. typhimurium strain TA98 with S9 mix. This strain, which is sensitive for frame-shift mutagens, was also employed in the experiments of Pool and Lin (1982) and of Florin et al. (1980) with negative results. Demerec et al. (1951) found phenol to be positive for reverse mutation in two strains of Escherichia coli without metabolic activation, when applied by treatment regimens that produced survival rates of <5%.

Phenol did not induce filamentation in an $ion^-$ mutant of E. coli (Nagel et al., 1982). Phenol was not found to have a significant effect on the induction of X-linked recessive lethal mutations in the Basc strain of D. melanogaster, nor was it found to induce micronuclei in mouse bone marrow when administered i.p. (Gocke et al., 1981).

In a Russian study, phenol increased the frequency of 8-azaguanine-resistant mutants at the HGPRT locus of the V79 Chinese hamster cell line, in the presence of mouse microsomes (Paschin and Bahitova, 1982). Concen-

TABLE 5-2

Genotoxicity Testing of Phenol

| Assay | Indicator/ Organism | Application | Concentration or Dose | Activating System | Response | Comment | Reference |
|---|---|---|---|---|---|---|---|
| Reverse mutation | Salmonella typhimurium TA1535 TA1537 TA98 TA100 | spot test | 2.3-2343 µg/ plate | ± S9 from Aroclor-induced rats | - | Toxic at 2343 µg/plate | Florin et al., 1980 |
| Reverse mutation | Salmonella typhimurium TA1535 TA1537 TA1538 TA98 TA100 | plate incorporation | 0-3600 µg/ plate | ± S9 from Aroclor-induced rats | - - - ± - | Data presented only for TA98. Position in the presence of S9 negative without activation. | Gocke et al., 1981 |
| Reverse mutation | Salmonella typhimurium TA1535 TA1537 TA1538 TA98 TA100 | plate incorporation | 0.5-5000 µg/ plate | ± S9 from Aroclor-induced rats | - | NC | Pool and Lin, 1982 |
| Reverse mutation | Salmonella typhimurium TA1535 TA1537 TA98 TA100 | plate incorporation with 30 minutes pre-inoculation | 0.0 µg/plate 33.0 100.0 333.0 1000.0 2500.0 3333.0 | ± S9 from Aroclor-induced rats or Aroclor-induced hamsters | - | Negative with activation regardless of source of enzymes. The phenol was dissolved either in water or DMSO. | Haworth et al., 1983 |
| Reverse mutation | Escherichia coli B/Sd-4/1,3, 4,5 B/Sd-4/3,4 | liquid incubation with plate incorporation | 0.08-0.20% | None | + | Reverse mutations to streptomycin independence with treatments that produce <5% survival | Demerec et al., 1951 |

TABLE 5-2 (cont.)

| Assay | Indicator/ Organism | Application | Concentration or Dose | Activating System | Response | Comment | Reference |
|---|---|---|---|---|---|---|---|
| Foward mutation | Escherichia coli lon⁻ strain | liquid culture | 10-500 µg/mL | ± S9 | - | No induction of filamentation | Nagel et al., 1982 |
| X-linked recessive lethal | Drosophila melanogaster (Basc strain) | adult feeding | 50 mM (see comment) | NA | - | One dose close to the $LD_{50}$ | Gocke et al., 1981 |
| Forward mutation | V79 Chinese hamster cell line | cell culture | 250-500 µg/mL | microsomal preparations from phenobarbital pretreated mice | + | As the number of 8-azaguanine resistant mutants increased; cell survival decreased<br>tions | Paschin and Bahtiova, 1982 |
| Micronucleus test | mouse bone marrow cells | intraperitoneal | 47-188 mg/kg | NA | - | NC | Gocke et al., 1981 |
| SCE | human lymphocytes | cell culture | 3 mM | ± S9 | +<br>+ | The positive response was inhanced with S9. | Morimoto et al., 1983 |
| DNA repair and replication inhibition | WI-38 human diploid fibroblasts | cell culture | 1 mM<br>10 mM | none<br>none | +<br>+ | DNA replication >50% inhibited<br>DNA repair synthesis 50% inhibited | Poirier et al., 1975 |
| DNA synthesis inhibition | HeLa cells | cell culture | 2 mM | S9 mix from Aroclor-induced rats | + | DNA synthesis inhibited | Painter and Howard, 1982 |

NA = Not applicable; NR = not reported; NC = no comment



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trations of phenol from 250-500 µg/mℓ significantly increased the numbers of 8-azaguanine resistant mutants; however, concentrations >250 µg/mℓ also had an effect on cell survival.

Without metabolic activation, a 3 mM concentration of phenol produced a small, but significant ($p<0.01$) increase in the frequency of SCEs after a 2-hour exposure of metaphase cells from human lymphocyte cultures (Morimoto et al., 1983). Metabolic activation with S9 mix produced a greater increase in SCEs ($p<0.001$).

Poirier et al. (1975) determined the effects of known cancer promoters on DNA repair synthesis and DNA replication in cultured human diploid fibroblasts (WI-38), after cells were damaged by the administration of the carcinogen, N-acetoxy-2-acetylaminofluorene, DNA replication was >50% inhibited at a phenol concentration of 1 mM and DNA repair was inhibited 50% at 10 mM (Poirier et al., 1975). Painter and Howard (1982) found that a 2 mM concentration of phenol, following activation by S9 mix from Aroclor-induced rats, produced inhibition of DNA synthesis in HeLa cells.

Phenol did not induce filamentation in a $lon^-$ mutant of E. coli (Nagel et al., 1982).

### 5.3. TERATOGENICITY

In two studies conducted by Jones-Price et al. (1983a,b), the teratogenicity of phenol was tested in Sprague-Dawley CD rats and CD-1 mice. Phenolin distilled water (0, 30, 60 or 120 mg/kg/day) was administered by gavage to timed-pregnant rats (23/group) on gestational days 6-15 (Jones-Price et al., 1983a). Day 0 of gestation was defined as the day on which vaginal smears were sperm-positive. The dams were killed on day 20 of gestation. Maternal weight gain during gestation, maternal liver weight and gravid uterine weight did not differ significantly between treated groups

and controls, nor were any other signs of maternal toxicity noted. A significant ($p<0.05$ or $p<0.01$) increase in the proportion of litters with resorption sites was observed at 30 and 60 mg/kg/day, respectively, but not at 120 mg/kg. There was no difference in the percentage of resorption per litter. It should be noted that the control group for this study exhibited zero reabsorptions, an unusual circumstance. Number of implantations was also significantly increased in the low and medium dose groups. In addition, in a preliminary teratology study conducted as part of the same research effort, no increase in the percent of litters with reabsorptions was seen at doses of 125 mg/kg and below. A significant trend for reduced fetal body weight was noted, but significant differences among treatment groups were not observed. In the authors discussion of this study the reduction of fetal body weight is presented as evidence of fetotoxicity. No mention of the proportion of litters with reabsorption sites is made. The proportion of litters with dead or malformed fetuses, the percentage of affected fetuses per litter, the number of live fetuses per live litter and the sex ratio of the litters did not differ significantly among dose-related groups; however, average fetal body weight per litter showed a significant dose-related ($p<0.001$) decrease; the difference between the high-dose group and controls was significant ($p<0.01$). Therefore, phenol produced selective fetal toxicity at levels that produced no maternal toxicity. No evidence of a structural teratogenic effect of phenol was observed.

In the concurrent study in CD-1 mice (Jones-Price et al., 1983b), phenol was administered by gavage to timed-pregnant animals (31-36/group) on gestational days 6-15, at doses of 0, 70, 140 and 280 mg/kg/day. The doses were selected following preliminary range-finding studies in which increased mortality (at $\geq$260 mg/kg/day), tremors and weight loss (at $\geq$200 mg/kg/day), statistically significant fetal growth retardation, decreased prenatal

viability and abnormal structural development (at ≥200 mg/kg/day) were observed. Day 0 of gestation was defined as the day on which copulation plugs were observed. The dams were killed on day 17 of gestation. Signs of maternal toxicity included increased mortality in the high-dose group (11 vs. 0% in other groups), and statistically significant dose-related trends for decreased body weight and gravid uterine weight that were significantly ($p<0.01$) lower in the high dose group compared with controls. Weight loss, tremors, ataxia, lethargy and irritability were also observed in the high-dose dams. No statistically significant differences among groups were observed for numbers of implantation sites per dam, prenatal viability or structural abnormalities of offspring. Mean fetal body weight per litter decreased in a dose-related manner ($p<0.001$) and was significantly lower than control for the high-dose group ($p<0.001$). Cleft palate was observed at incidences of 0/308, 1/290, 1/280 and 8/214 in the control, 70, 140 and 280 mg/kg/day groups, respectively. The incidence in the high-dose group was not significantly different from control, but the incidence of cleft palate in historic controls was 1/1580. The effects on fetuses occurred at doses that were toxic to dams, and are probably the secondary effects of increased maternal stress.

Minor and Becker (1971) administered phenol (20, 63 or 200 mg/kg/day) i.p. to Sprague-Dawley rats on days 9-11 or 12-14 of gestation. No teratogenic effect was observed, but fetotoxicity at the highest dose (evidenced by decreased fetal body weight with respect to controls) resulted from exposure on days 12-14 of gestation.

In a study by Korshunov (1974) from the Russian literature, an unspecified strain of rats inhaled 5.06 or 0.51 mg/m³ of phenol (exposure regimen not reported) throughout pregnancy. Exposure resulted in an increased incidence of preimplantation losses and early postnatal death of the offspring.

## 5.4. OTHER REPRODUCTIVE EFFECTS

Heller and Pursell (1938) administered phenol continuously at concentrations of 100-12,000 ppm in the drinking water to rats for 5 generations (Table 5-3). No effects were observed at ≤5000 ppm for 3 generations or ≤1000 ppm for 5 generations; at 7000 ppm for 2 generations, offspring growth was stunted; at 8000 ppm, dams were irritable and failed to care for their pups, many of which died; at 10,000 ppm, reproduction was retarded and offspring died at birth; and at 12,000 ppm, reproduction ceased. No additional details were reported.

## 5.5. SUBCHRONIC AND CHRONIC TOXICITY

Information regarding the effects on humans of repeated oral exposure to phenol is limited. In 1974, an accidental spill of 100% phenol caused groundwater contamination in a rural area of southern Wisconsin (Baker et al., 1978). Seventeen people who had used the contaminated water for ~1 month at an estimated intake of 10-240 mg/person/day reported symptoms of diarrhea, mouth sores, dark urine and burning of the mouth. The reported illnesses prompted a systematic evaluation of the exposed population, conducted ~7 months after the spill. The study group consisted of 39 individuals who lived 120-310 m from the spill and had >0.1 mg phenol/ℓ in their drinking water. The control group consisted of 119 individuals who lived 210 m-1.9 km from the spill and had 0-0.1 mg phenol/ℓ in their drinking water. Individuals in the study population were given questionnaires for reporting symptoms, water intake history, water quality comments and other demographic information. The questionnaires included symptoms not related to the known effects of phenol in an attempt to identify psychosomatic complaints. Exposure assessments were based on water monitoring starting immediately after the spill and continuing for 7 months. The limit of detection for phenol was 0.001 mg/ℓ.

TABLE 5-3

Subchronic and Chronic Oral Toxicity of Phenol

| Species | No. of Animals | Dose | Route | Length of Exposure | Effects | Reference |
|---|---|---|---|---|---|---|
| Mice B6C3F1 | 10M, 10F per group | 0, 100, 300, 1000, 3000, 10,000 ppm | oral in drinking water | 90 days | No effects noted from 0-3000 ppm in any parameter studied (body weight, appearance, behavior, food and water consumption, histological examination of tissues). At 10,000 ppm decreased water consumption, decreased weight gain (80% less in males, 33% less in females), no histopathological changes | NCI, 1980 |
| | 50M, 50F | 2500 ppm | oral in drinking water | 103 weeks | Decreased weight gain, decreased water consumption (75% of control) | |
| | 50M, 50F | 5000 ppm | oral in drinking water | 103 weeks | Decreased weight gain, decreased water consumption (50-60% of control) | |
| Rats F344 | 10M, 10F per group | 0, 100, 300, 1000, 3000, 10,000 | oral in drinking water | 90 days | No effects noted from 0-3000 ppm in any parameter studied (see above). At 10,000 ppm decreased water consumption, decreased weight gain (16% less in males, 26% less in females), no histopathological changes. | |
| | 50M, 50F | 2500 ppm | oral in drinking water | 103 weeks | Decreased mean body weight gain, decreased water consumption (80% of control) | |
| | 50M, 50F | 5000 ppm | oral in drinking water | 103 weeks | Decreased mean body weight gain, decreased water consumption (90% of control), chronic kidney inflammation in male ($p \leq 0.00191$) and female ($p \leq 0.00001$, Fisher's Exact Test) rats. | |
| Rats | NR | 0, 800, 1200* 1600, 2000, 2400 mg/L | oral in drinking water | 12 months | Weight gain depressed at two highest dose levels. No other significant differences noted between control and experimental animals. | Deichmann and Oesper, 1940 |

TABLE 5-3 (cont.)

| Species | No. of Animals | Dose | Route | Length of Exposure | Effects | Reference |
|---|---|---|---|---|---|---|
| Rats | NR | 100 mg/kg 5 days/week | oral (gavage) | 6 months | Slight liver changes and slight to moderate kidney damage | Dow Chemical Company, 1945 |
| | NR | 50 mg/kg/day 5 days/week | oral (gavage) | 6 months | Slight kidney damage | |
| Rats | NR | 100-1000 ppm | oral in drinking water | 5 generations | No deleterious effect | Heller and Pursell, 1938 |
| | NR | 3000-5000 ppm | oral in drinking water | 3 generations | No significant effect | |
| | NR | 7000 ppm | oral in drinking water | 2 generations | Below normal growth in young | |
| | NR | 8000 ppm | oral in drinking water | 2 generations | Decreased water intake, occasional irritability, impaired mothering behavior, many young died, below normal growth rate | |
| | NR | 10,000 ppm | oral in drinking water | NR | Offspring died at birth, retarded growth rate | |
| | NR | 12,000 ppm | oral in drinking water | NR | Retarded growth rate, no reproduction, mature animals died in hot weather | |
| Rats | NR | 200 mg/kg/day | oral (gavage) | 20 daily doses | Slight liver and kidney effects | Dow Chemical Company, 1945 |
| | NR | 100 mg/kg/day 10 mg/kg/day | oral (gavage) | 20 daily doses | No liver or kidney effects noted | |

*The concentrations correspond to average intakes of 0, 21, 30, 49, 56 and 55 mg/rat/day, respectively, based on actual water consumption data.

NR = Not reported

The results of the evaluation of symptoms are presented in Table 5-3. Statistically significant differences between groups included incidences of diarrhea, mouth sores and burning mouth, which were reported at higher rates in the phenol-exposed group. Further, there was a clear temporal association between the onset of symptoms and phenol contamination in the exposed group. In the control group, symptoms were reported to have occurred randomly over the 7-month period. Approximately 6 months after the initial exposure, no significant differences between the two groups were noted based on analyzed serum concentrations of SGOT, bilirubin, creatinine, uric acid, glucose and cholesterol, as well as urinalysis including urine levels of phenol. The results of the analysis are presented in Table 5-4.

Four subchronic oral studies on the toxicity of phenol to animals were located in the literature (see Table 5-3). In an unpublished study conducted by Dow Chemical Company in 1945, phenol was administered to rats at 10, 100 and 200 mg/kg bw/day by gavage in 20 daily doses. Rats at the highest dose level showed slight liver and kidney effects; however, no effects were noted at the lower dose levels. In subsequent tests, rats received 135 doses of 50 and 100 mg phenol/kg bw, 5 days/week by gavage, over a 6-month period. Nc effect on growth rate was noted when treated and control animals were compared. At 100 mg/kg (71.4 mg/kg/day, TWA), slight liver changes and slight to moderate kidney damage were noted; at 50 mg/kg (37.5 mg/kg/day, TWA), only slight kidney damage was observed.

A 90-day range-finding study was conducted in F344 rats and B6C3F1 mice to determine the concentrations of phenol that would be used in a subsequent 2-year carcinogenesis study (NCI, 1980) (details summarized in Table 5-3). Phenol was admininstered in the drinking water at five concentrations (100, 300, 1000, 3000 and 10,000 ppm) over a 90-day exposure period. Control

TABLE 5-4

Symptom Distribution of Cases of Human Ingestion of Phenol and Controls[a]

| Symptom | % of Individuals with Symptom | |
|---|---|---|
| | Study Group (n=39) | Control Group (n=119) |
| Vomiting | 15.4 | 13.9 |
| Diarrhea | 41.0[b] | 13.5 |
| Headache | 23.1 | 16.1 |
| Skin rash | 35.9 | 22.6 |
| Mouth sores | 48.7[b] | 12.6 |
| Paresthesia or numbness | 13.2 | 8.4 |
| Abdominal pain | 23.1 | 11.8 |
| Dizziness | 21.1 | 9.3 |
| Dark urine | 17.9 | 3.4 |
| Burning with urination[c] | 10.3 | 10.0 |
| Fever[c] | 15.4 | 10.9 |
| Back pain | 20.5 | 11.0 |
| Burning mouth | 23.1[b] | 6.8 |
| Shortness of breath | 10.3 | 6.7 |

[a] Source: Baker et al., 1978

[b] Significantly greater than controls, $p<0.01$, Fisher's Exact Test

[c] Not associated with phenol exposure in previous medical reports

group animals received 0 ppm phenol. Groups consisted of 10 rats and 10 mice of each sex, and weekly records were made of body weight, appearance, behavior and food and water consumption. All animals were sacrificed at 13 weeks and comprehensive microscopic examinations were conducted. At the four lowest dose levels, no effects were noted in either species, in any of the parameters studied. At 10,000 ppm, males and females of both species rejected water and exhibited decreased weight gain. No other effects were reported.

Two additional subchronic oral studies in white mice are available as English abstracts from the Polish literature. Daily oral administration of phenol over a 5-month period at 0.04, 0.9 or 9 mg/kg bw/day resulted in dose-related histoenzymic and morphological changes in the liver (Peziol-Laszczynska et al., 1981). Daily oral administration over a 5-month period of 8.33 mg/kg/day caused droplet-hyaline and vacuolar degeneration of renal tubule cells (Wozniak et al., 1981). The cell morphology was said to be "affected less" by the lower dose levels (0.83 and 0.08 mg/kg/day). Because the quality of these studies cannot be documented and because the reported results contradict the results of other studies that are of high quality, these studies are not given further consideration.

Three studies regarding chronic toxicity resulting from oral exposure to phenol were located in the available literature. In the NCI (1980) bioassay (see Section 5.1.) in which phenol was administered through the drinking water of rats and mice at 0, 2500 and 5000 ppm, the only adverse effects observed were a dose-related decrease in weight gain of rats and mice that was thought to result from decreased water consumption, and an apparently treatment-related increase in the incidence of chronic kidney inflammation in high-dose male and female rats. The incidences in male rats were as follows: control, 37/50; low-dose, 37/50; high-dose, 48/50; and in

female rats: control, 7/50; low-dose, 13/50; high-dose, 28/50. Statistical tests to measure the significance of these incidences were not reported by the authors; however, the Fisher Exact Test revealed highly significant differences: ($p=0.00191$) for the incidence in high-dose males and ($p=0.00001$) for the incidence in high-dose females.

The second study was a report from the early literature (see Section 5.4.) in which phenol was administered to rats in the drinking water for up to 5 generations at dose levels ranging from 100-12,000 ppm (Heller and Pursell, 1938). The observed effects are presented in Table 5-3.

In the third study (Deichmann and Oesper, 1940), phenol was administered to rats through their drinking water for 12 months at levels that corresponded to an average intake of phenol of 0, 21, 30, 49, 56 and 55 mg/rat/day based on actual water consumption data (0, 800, 1200, 1600, 2000 and 2400 ppm, respectively, in the water). The only effect noted was decreased weight gain at the two highest dose levels.

Subchronic inhalation studies in experimental animals are summarized in Table 5-5. Deichmann et al. (1944) exposed guinea pigs (12), rabbits (6) and rats (15) to phenol vapors ranging in concentration from 100-200 $mg/m^3$. After 20 exposures over a 28-day period, five guinea pigs died; the remaining guinea pigs were killed after 29 exposures. Guinea pigs exhibited both internal and external signs of toxicity (Table 5-5). After 63 exposures over an 88-day period, rabbits exhibited no external signs of toxicity, but manifested lung, liver and kidney damage less severe than that in guinea pigs. After 53 exposures over 74-day period, rats showed no external or internal signs of toxicity.

Rats (50), monkeys (10) and mice (100) were exposed to phenol at a concentration of 19 $mg/m^3$ [corresponding to the TWA-TLV recommended by

TABLE 5-5

Subchronic Inhalation Toxicity of Phenol

| Species | No. of Animals | Dose | Length of Exposure | Effects | Reference |
|---|---|---|---|---|---|
| Mice | 100 treated, 100 controls | 19 mg/m³ (5 ppm) | 8 hours/day, 5 days/week, 90 days | increased stress test endurance ($p<0.05$), no significant differences seen in any other parameters studied (hematology, urinalysis, blood chemistry, kidney function, rate of gain, pathological examination) | Sandage, 1961 |
| Rats | 15 treated, no controls | 100-200 mg/m³ (26-52 ppm) | 7 hours/day, 5 days/ week, 74 days, 53 exposures | no external or internal signs of toxicity | Deichmann et al., 1944 |
| Rats | 50 treated, 50 controls | 19 mg/m³ (5 ppm) | 8 hours/day, 5 days/ week, 90 days | slight weight gain with respect to controls ($p<0.05$), no significant differences seen in any other parameters studied (hematology, urinalysis, blood chemistry, kidney function, stress tests, pathological examination) | Sandage, 1961 |
| Guinea pigs | 12 treated, no controls | 100-200 mg/m³ (26-52 ppm) | 7 hours/day, 5 days/ week, 29 exposures | decreased activity, weight loss, respiratory difficulties, hind quarter paralysis; histological changes included myocardial necrosis, acute lobular pneumonia, liver and kidney damage; 5/12 deaths | Deichmann et al, 1944 |
| Rabbits | 6 treated, no controls | 100-200 mg/m³ (26-52 ppm) | 7 hours/day, 5 days/ 88 days, 63 exposures | no external signs of toxicity; histological changes included lobular pneumonia, purulent bronchitis, myocardial degeneration and necrosis, liver and kidney damage | Deichmann et al, 1944 |
| Monkeys | 10 treated, 10 controls | 19 mg/m³ (5 ppm) | 8 hours/day, 5 days/ week, 90 days | slight weight gain with respect to controls ($p<0.05$), no significant difference seen in any other parameters studied (hematology, urinalysis, blood chemistry, kidney function, stress tests, pathology) | Sandage, 1961 |



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ACGIH (1980)], 8 hours/day, 5 days/week for 90 days (Sandage, 1961). Hematology tests, urinalysis, blood chemistry tests, kidney function tests, stress tests and weight measurements were performed periodically over the course of the study. Pathological examinations were performed at autopsy. No significant adverse toxic effects were noted when treated animals were compared with controls.

In a study from the Russian literature in which rats (15/group) were exposed to 3 dose levels of phenol vapors (0.011, 0.11 and 5.2 mg/m$^3$) continuously for 61 days, Mukhitov (1974) observed changes in blood cholinesterase activity and time for excitation of extensor muscles (0.11 mg/m$^3$ and 5.2 mg/m$^3$) and decreased weight gain (5.2 mg/m$^3$). Rats exposed to 0.011 mg phenol/m$^3$ did not differ from controls, within the parameters of the study.

In a short-term study, Dalin and Kristoffersson (1974) exposed white rats (males and females, ~300 g) to 0 or 100 mg phenol/m$^3$ continuously for 15 days and determined the effects on the central nervous system, some blood parameters and weight. Treated rats exhibited mild behavioral effects from days 1-5 of exposure. After 15 days of exposure, there was a significant decrease in the ability of treated rats to cling to a tilting plane, as compared with controls. This test is presumed to measure a variety of CNS effects including vestibular and grasping reflexes. Hemoglobin and hematocrit values and plasma $Na^+$, $Ca^{2+}$ and $Cl^-$ levels were not affected by treatment. $K^+$ and $Mg^{2+}$ levels were increased significantly as were the activities of lactate dehydrogenase, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase and glutamate dehydrogenase. No significant treatment-related effect on weight was observed.

## 5.6. OTHER RELEVANT INFORMATION

The signs and symptoms of acute phenol toxicity depend on the route of exposure and are similarly manifested in man and experimental animals (U.S. EPA, 1983). CNS effects such as muscular weakness, muscle twitches, general tremors, convulsions and coma have been observed in a number of species including rabbits, rats, cats and humans (Diechmann and Keplinger, 1981; Liao and Oehme, 1981; Diechmann and Witherup, 1944).

The oral $LD_{50}$ of phenol is 530-650 mg/kg in rats (Deichmann and Witherup, 1944; Flickinger, 1976), 300 mg/kg in mice (Von Oettingen and Sharpless, 1946), 400-600 mg/kg in rabbits (Deichmann and Witherup, 1944), 100 mg/kg in cats (Macht, 1915) and 500 mg/kg in dogs (Macht, 1915).

Coan et al. (1982), in a study on the direct effect of phenol on the rat kidney, measured glomerular filtration rates, effective renal plasma flow, $Na^+$ and $K^+$ reabsorption and urine flow rate during 100-minute infusions of phenol (0.1, 1.0 or 5.0% made isotonic with NaCl; infusion rate of 20.6 µL/minute) using a catheter positioned between the right renal and coeliac arteries. When analyzed by variance, phenol treatment had no effect on the parameters of renal hemodynamics listed above; however, consistent, dose-related histological effects were observed. Kidneys of animals infused with 0.1% phenol were histologically similar to controls; kidneys of animals receiving 1.0% phenol showed significant alterations; at 5.0% phenol, there was extensive vacuolization and sloughing of proximal tubules in addition to necrotic glomeruli.

Murphy et al. (1982), studying ocular irritancy in rabbits produced by acids and basis of various pHs, found that 5% solutions of phenol (pH 7.7) applied to the eyes of rabbits produced corneal opacities in nearly all treated eyes. Washing the eyes 30 seconds after treatment with phenol reduced the amount of damage observed.

A 2.5% solution of phenol was applied to a 5 mm section of the surgically exposed sciatic nerve of five male Sprague-Dawley rats (175-250 g) (Anderson, 1983). After a 15-minute exposure, the area was flushed with 20 mL of saline. Three weeks after exposure, three of the treated animals exhibited signs of peripheral neuropathy as shown by loss of foot placement, slowing of the compound action potential and a reduction in the amplitude recorded from these nerves, and a prolonged relative refractory period.

In a study designed to determine the effect of phenol on organelle membranes of cultured cells, cover slips on which cells were growing were incubated for 1 hour in 5 mL of medium containing final concentrations of phenol of 1 or 2 mg/mL (Tyas, 1978). Lysosomal membranes were found to be labilized by this procedure, and mitochondrial membranes exhibited increased permeability.

In an effort to determine the relative efficacy of various recommended first aid treatments after dermal exposure to phenol, Conning and Hayes (1970) found the dermal $LD_{50}$ in female rats (Alderley Park specific pathogen-free strain) to be 0.625 mL reagent grade phenol/kg bw. Dilutions of phenol with various vehicles were found to be more toxic than undiluted phenol, depending on both the dilution factor and the vehicle. For example, 0.5 mL/kg of a 66% phenol/water solution produced death in all five exposed rats within 5 hours of administration, compared with only one death in the group receiving 0.5 mL/kg of undiluted phenol. The most effective therapeutic treatment was found to be swabbing the exposed area with olive oil, glycerol or propylene glycol.

Amoore and Hautala (1983) reported that the air odor threshold for phenol (determined as the geometric average of all available literature data) was 0.04 ppm (v/v). Comparing this with the TLV of 5 ppm (19 mg/m³) established by ACGIH (1980), they concluded that 50-90% of "distracted" persons would perceive the odor of phenol at or below the TLV.

## 6. AQUATIC TOXICITY

This review of toxic effects of phenol has been limited to those reported for aquatic species common to the United States.

### 6.1. ACUTE TOXICITY

The acute lethal effects of phenol have been determined in a number of cold and warm freshwater fish. The rainbow trout, Salmo gairdneri, had a 96-hour $LC_{50}$ value of 8.9 mg phenol/ℓ (DeGraeve et al., 1980a). The 48-hour $LC_{50}$ in the harlequin fish, Rasboro heteromorpha, was between 6.8 and 7.4 mg phenol/ℓ (Alabaster, 1969). Miller and Ogilvie (1975) determined a 24-hour $LC_{50}$ of 11.7 mg/ℓ for the brook trout, Salvelinus fontinalis. Millemann et al. (1984) reported a 96-hour $LC_{50}$ value of 25.6 mg phenol/ℓ for the fathead minnow, Pimephales promelas. Phipps et al. (1981) reported a static 48-hour $LC_{50}$ of 8.3 mg phenol/ℓ and a flow-through 96-hour $LC_{50}$ of 28 mg/ℓ in fathead minnows. In fry, juvenile and subadult stages of fathead minnows, 96-hour $LC_{50}$ values of 23.0, 43.7 and 31.2 mg phenol/ℓ, respectively, were reported (Mayes et al., 1983). Mattson et al. (1976) reported 1-, 24- and 48-hour $LC_{50}$ values to be >50 mg phenol/ℓ; 72- and 96-hour $LC_{50}$ values were 33 and 32 mg/ℓ, respectively, in fathead minnows. The 48- and 96-hour $LC_{50}$ values determined in fathead minnows exposed at 15°C were 41 and 36 mg/ℓ, while testing at 25°C resulted in values of 28 and 24 mg phenol/ℓ, respectively (Ruesink and Smith, 1975). The threshold concentrations for lethality were 27 and 22 mg/ℓ, respectively, at 15 and 25°C (Ruesink and Smith, 1975). DeGraeve et al. (1980b) reported 96-hour $LC_{50}$ values of 67.5 and 24.9 mg phenol/ℓ for tests in fathead minnows exposed at 14 and 25°C, respectively. The 48-hour $LC_{50}$ values for the goldfish, Carassius auratus, and the golden orfe, Leuciscus idus melanotus, were 46 and 25 mg phenol/ℓ, respectively

(Bridie et al., 1979; Juhnke and Luedemann, 1978). Sliger (1975) reported a 48-hour $LC_{50}$ value of 82 mg/ℓ for channel catfish, Ictalurus punctatus, when phenol was introduced gradually and 31 mg/ℓ when fish were placed in predetermined phenol solutions.

Pathological effects of acute exposure to phenol determined in rainbow trout included hematological changes (Swift, 1981), inflammation, hemorrhage and necrosis of the gills, and pharynx and splenic swelling (Mitrovic et al, 1968).

The 24-hour $LC_0$, $LC_{50}$ and $LC_{100}$ values for the water flea, Daphnia magna, were 3.9, 31 and 125 mg phenol/ℓ (Bringmann and Kuehn, 1977) or 3.1, 12 and 100 mg/ℓ, respectively (Bringmann and Kuehn, 1982). DeGraeve et al. (1980a) reported that the 48-hour $LC_{50}$ for D. pubicaria was >109 mg phenol/ℓ. For the amphipods, Gammarus pulex and G. minus, 48-hour $LC_{50}$ values were 55-89 mg/ℓ (in soft and hard water) and 37.4 mg/ℓ, respectively (Stephenson, 1983; Millemann et al., 1984). The 48-hour $LC_{50}$ values for three species of chironomid midges ranged from 72.7-187.2 (Franco et al., 1984; Millemann et al., 1984). In five species of freshwater snails, 48-hour $LC_{50}$ values ranged from 107-320 mg phenol/ℓ.

The 24- and 48-hour $LC_{50}$ values for the marine brine shrimp, Artemia salina, were 157 and 56 mg phenol/ℓ, respectively. McLeese et al. (1979) reported the lethality threshold for the shrimp, Crangon septemspinosa, was 7.5 mg phenol/ℓ for a 21-hour exposure. Buikema et al. (1981) reported 24-, 48- and 96-hour $LC_{50}$ values of 14.4, 12.8 and 12.5 mg/ℓ for myrid shrimp, Mysidopsis bahia, exposed to phenol. The 48-hour $LC_{50}$ for a marine polychaete, Ophryotrocha diaderma, was determined to be between 33 and 100 mg phenol/ℓ (Parker, 1984).

## 6.2. CHRONIC EFFECTS

The $LC_{50}$ value determined for fathead minnows, P. promelas, exposed for 192 hours was 23 mg phenol/ℓ (Phipps et al., 1981). In rainbow trout (S. gairdneri), zebrafish (Brochydanio rerio) and flagfish (Jordanella floridae), 10-day toxicity threshold concentrations were 11.6, 29.0 and 36.3 mg phenol/ℓ, respectively (Fogels and Sprague, 1977). Mitrovic et al. (1968), however, reported gill damage and pathological changes in the liver, kidney, spleen, small intestine, ovary and skin in rainbow trout exposed to 6.5-7.3 mg phenol/ℓ for up to 7 days.

The 7-day $LC_{50}$ value for embryo/larval stage largemouth bass, Micropterus salmoides, was 2.67 mg phenol/ℓ (Millemann et al., 1984). In rainbow trout, a 27-day $LC_{50}$ for embryo/larval stages was 0.12 mg phenol/ℓ (Millemann et al., 1984). In fathead minnow and rainbow trout fry, significant growth reduction was evident following exposure at 2.5 and 0.20 mg phenol/ℓ, respectively, for up to 58 days (DeGraeve et al., 1980b). Holcombe et al. (1982) also reported growth inhibition in fathead minnow larvae exposed at 1.83-3.57 mg phenol/ℓ for up to 4 weeks. Based on mortality of carp larvae, Cyprinus carpio, exposed to phenol for 4 days, Verma et al. (1981) suggested an MATC of between 0.11 and 0.13 mg/ℓ.

## 6.3. PLANT EFFECTS

The toxicity threshold levels of phenol, causing initial inhibition of cell multiplication, for the blue green alga (Microcystis aeruginosa) and green alga (Scenedesmus aeruginosa) were 4.6 and 7.5 mg/ℓ, respectively (Bringmann and Kuehn, 1978a,b, 1980). The $EC_{50}$ values for 50% decreased carbon assimilation in the green algae, Selenostrum capricornutum, and the diatom, Nitzschia palea, were 287 and 185 mg phenol/ℓ, respectively (Millemann et al., 1984). The toxicity threshold for decreased cell multi-

plication in S. capricornutum was ~20 mg phenol/ℓ regardless of whether static or dynamic cultures were treated (Klaine and Ward, 1983).

In higher aquatic plants, Stom and Roth (1981) reported complete growth inhibition in Dunaliella salina following 15 minutes of exposure at 0.941 g phenol/ℓ. In Nitella, cytoplasmic streaming was inhibited completely following 15 minutes of exposure at 2.823 g phenol/ℓ. A 50% reduction of growth in Elodea canadensis occurred within 9 days when exposed to 0.234 g phenol/ℓ. Plant multiplication was decreased by 50% in Lemna minor following 12 days of exposure to 0.169 g phenol/ℓ (Stom and Roth, 1981).

## 6.4. RESIDUE

Specific data regarding residues of phenol in aquatic organisms or sediments were not available. The persistence and fate of phenol in water was discussed in Section 2.1. Briefly, the rate of biodegradation, photolysis and evaporative loss of phenol reduces the risk of accumulation of phenol in the aquatic environment. There does appear to be a higher potential for phenol accumulation in marine waters, since its degradation there may be slower (Lee and Ryan, 1979).

## 6.5. OTHER RELEVANT INFORMATION

The effects of phenol on aquatic microorganisms have been tested in bacteria, yeast and protozoans. Toxicity levels for bacteria ranged from 4.7-64 mg phenol/ℓ (Bulich, 1979; Bulich et al., 1981; Bringmann and Kuehn, 1976, 1980; Denyer et al. 1980). Yeast were much more resistant, showing a 50% decrease in growth at 460-500 mg phenol/ℓ (Kwasniewska and Kaiser, 1983). For a number of protozoan species, toxic and lethal levels ranged from 5-95 mg phenol/ℓ (Bringmann and Kuehn, 1980; Honig et al., 1980; Schultz and Dumont, 1977).

# 7. EXISTING GUIDELINES AND STANDARDS

## 7.1. HUMAN

The TWA-TLV adopted by ACGIH (1980) for phenol is 5 ppm (19 mg/m$^3$), based primarily on the results of Deichmann et al. (1944) (see Section 5.5.). The OSHA standard for phenol (Code of Federal Regulations, 1981) is the same as are most of the published hygienic standards for other countries (East and West Germany, Sweden, Czechoslovakia) (ACGIH, 1980).

U.S EPA (1980) listed the ADI (currently RfD) for phenol as 7.0 mg/day based on a rat subchronic to chronic LOAEL associated with slight kidney damage and using an uncertainty factor of 500. For the purpose of comparison, the U.S. EPA (1980) also estimated a level of phenol of 0.3 mg/ℓ for controlling undesirable taste and odor of ambient water.

## 7.2. AQUATIC

The U.S. EPA (1980) suggested that acute and chronic toxicity would occur in freshwater aquatic organisms at 10.2 and 2.56 mg phenol/ℓ, respectively. Acute toxicity in marine organisms occurred at concentrations as low as 5.8 mg/ℓ. These levels were suggested as criteria for aquatic life, but it was emphasized that these concentrations may cause toxic effects in more sensitive species.

## 8. RISK ASSESSMENT

The carcinogenicity of phenol administered in the drinking water at 2500 or 5000 ppm to rats and mice has been studied with equivocal results (NCI, 1980). Increased incidences (see Table 5-1) of pheochromocytomas of the adrenal medulla and leukemias or lymphomas were observed in male rats at 2500 ppm, but not at 5000 ppm. No increased tumor incidences were observed in female rats or in mice. Although the increased incidence in low dose rats was possibly treatment-related, NCI (1980) concluded that phenol was not carcinogenic under the conditions of the biossay.

Phenol has been found to be a tumor promotor (Boutwell and Bosch, 1959; Salaman and Glendenning, 1957) and a weak whole carcinogen when applied dermally to mice (Boutwell and Bosch, 1959), but not a cocarcinogen with benzo(a)pyrene in mice (Van Duuren and Goldschmidt, 1976; Van Duuren et al., 1971, 1973).

Mutagenicity testing of phenol has been performed with a variety of organisms and experimental protocols. Data from the early literature regarding reverse mutation assays in E. coli (Demerec et al., 1951) indicated that phenol is capable of causing mutations, but results of reverse mutation assays in S. typhimurium and recessive-lethal assays in D. melanogaster from the later literature generally have not supported this (Haworth et al., 1983; Pool and Lin, 1982; Florin et al., 1980; Gocke et al., 1981). In mammalian systems, phenol has also produced equivocal results, being negative in the micronucleus test in mouse bone marrow cells (Gocke et al., 1981) and positive for SCE in human lymphocytes in culture (Morimoto et al., 1983). Phenol was positive for inhibition of DNA replication and DNA repair synthesis in human diploid fibroblasts and in HeLa cells (Poirier et al., 1975; Painter and Howard, 1982).

Phenol was not teratogenic to the offspring of rats treated during gestation at gavage doses ≤120 mg/kg/day (Jones-Price et al., 1983a). Fetotoxicity, however, was evidenced by a significant dose-related ($p<0.001$) decrease in mean fetal body weight per litter that was significantly different ($p<0.01$) between the 120 mg/kg/day group and controls. No signs of maternal toxicity were observed at ≤120 mg/kg/day. Phenol administered by gavage to pregnant mice resulted in growth retardation, decreased prenatal viability, abnormal structural development and an increased incidence of cleft palate at dosages (≥200 mg/kg/day) that were toxic to dams (death, tremors and weight loss) (Jones-Price et al., 1983b). No significant differences were observed in mouse offspring or dams at ≤140 mg/kg/day.

No effects on reproduction of rats were observed at ≤5000 ppm phenol in the drinking water for 3 generations or ≤1000 ppm for 5 generations (Heller and Pursell (1938). At 7000 ppm, offspring had retarded growth and at 8000 ppm, dams failed to care for the pups, resulting in death of the offspring. Reproduction was retarded at 10,000 ppm and was completely inhibited at 12,000 ppm.

Further information on effects of repeated and long-term exposure to phenol was available from an epidemiologic study in humans exposed to phenol in their drinking water following an accidental spill and from subchronic and chronic studies in experimental animals. In the epidemiologic study, persons who had been drinking the contaminated water for ~1 month at an estimated daily intake of 10-240 mg/day reported such symptoms as diarrhea, burning mouth, mouth sores and dark urine, prompting a systematic evaluation of the exposed population (Baker et al, 1978). This evaluation took place ~7 months after the spill. Persons living in proximity to the spill site with levels of phenol in the drinking water of >0.1 mg/ℓ had significantly

($p<0.01$) greater incidences of diarrhea, mouth sores and burning mouth than did controls with 0-0.01 mg/ℓ of phenol in their water supply.

In subchronic studies, slight kidney damage was observed in rats treated by gavage at 50 mg/kg, 5 days/week for 6 months (TWA=35.7 mg/kg/day) and slight liver and moderate kidney damage was observed at 100 mg/kg (TWA=71.4 mg/kg/day) (Dow Chemical Company, 1945); however, no effects on livers, kidneys or any other organ were observed in 90-day studies in rats and mice at drinking water concentrations of 10,000 ppm phenol (~780 mg/kg/day for rats and ~1700 mg/kg/day for mice, assuming that rats and mice consume a daily amount of water equal to 7.8 and 17% of their body weight, respectively) (NCI, 1980). At 10,000 ppm, reduced water intake and decreased body weight were observed. Decreased weight gain and reduced water intake were also observed in rats and mice exposed at drinking water concentrations of phenol of 2500 and 5000 ppm for 103 weeks and observed for an additional 2 weeks (NCI, 1980). In addition, male and female rats at 5000 ppm had statistically significant increased incidences of chronic kidney inflammation. These exposures correspond to 153 and 344 mg/kg/day, respectively, for rats and 313 and 459 mg/kg/day, respectively, for mice. The equivalent doses were calculated by multiplying the concentration by 103 weeks/105 weeks, by the assumed fraction of the body weight consumed daily as water (7.8% for rats, 17% for mice) and by the percentage of decreased water consumption compared with controls (90% for high-dose rats, 80% for low-dose rats, 75% for high-dose mice and 55% for low-dose mice).

No adverse effects were observed in mice, rats or monkeys exposed by inhalation to phenol at 5 ppm (19 mg/m$^3$), 8 hours/day, 5 days/week for 90 days (Sandage, 1961). The exposure is equivalent to a human dose of 0.64 mg/kg/day or 45 mg/day for a 70 kg man, assuming a human inhalation rate of 20 m$^3$/day and 50% absorption. Inhalation exposures of 100-200 mg/m$^3$,

7 hours/day, 5 days/week for up to 88 days resulted in hypoactivity, weight loss, respiratory difficulties, hind leg paralysis and death in guinea pigs, histopathologic changes in the myocardium, lungs, liver and kidney of guinea pigs and rabbits, but no effects in rats (Deichmann et al., 1944). Using the assumptions previously described, 100 mg/m$^3$, 7 hours/day, 5 days/week, is equivalent to a human dose of 3.0 mg/kg/day or 208 mg/day for a 70 kg man.

An ADI (currently RfD) value of 7.0 mg/day has been estimated previously by U.S. EPA (1980) based on the LOAEL of 50 mg/kg/dose in 135 doses by gavage over 180 days in rats for slight kidney damage in the study reported in the research report by Dow Chemical Company (1976). However, this report did not mention about the dosing regimen which covered only 5 days/week as stated in the original report (Dow Chemical Company, 1945). Therefore, the 50 mg/kg dose can be expanded to 35.7 mg/kg/day on a 7-day basis.

In 1-year studies in which rats were exposed to phenol in drinking water, Deichmann and Oesper (1940) noted no effects on water consumption and weight gain at phenol concentrations as high as 1600 mg/ℓ. Further, in studies using rats and spanning 3-5 generations, Heller and Purcell (1938) observed normal growth and reproduction at concentrations up to 5000 mg/ℓ. Thus, with this data base alone, 1600 mg/ℓ would be a reasonable NOEL on which to base an ADI that would be considered protective of histopathologic and reproductive effects. Taking the drinking water consumption data provided by Deichmann and Oesper (1940) for the 1600 mg/ℓ group, this NOEL represents an average dose of 49 mg/kg/day.

A recent teratogenicity study by Jones-Price et al. (1983a) found a significant dose-related decrease in average fetal body weights in rats, although the decrease was significantly different from controls only in the high-dose (120 mg/kg) group and the magnitude of the decrease was slight (92.8% of controls).

Baker et al. (1978) reported an incident in which humans were exposed to phenol in drinking water following an accidental spill. In this incident, concentrations of phenol in well water during the period in which contaminated water was consumed ranged from 0.21-126 mg/ℓ. Based on these measurements and histories of water usage, individuals exhibiting symptoms of diarrhea and buccal irritation were estimated to have consumed phenol at daily doses of 10-240 mg. Individuals were not surveyed until 7 months after the incident. The symptoms reported were all nonspecific and the amount of phenol ingested was unknown.

The differences in LOAELs of the NCI (1980) chronic study (344 mg/kg) and Dow (1976) subchronic study (50 mg/kg) are plausibly attributed to differences in mode of administration with the gavage study of Dow producing the lowest LOAEL. Although the drinking water administration studies would be expected to more closely approximate human exposure patterns, the reported effects on fetal body weight at lower doses (120 mg/kg) than the NCI NOAEL (Jones-Price et al., 1983a) must be considered. Studies where prenatal development has been evaluated following administration of phenol in the drinking water have not been reported. Early, multi-generation drinking water studies have been conducted and indicate that effects on reproductive performance and postnatal survival and growth do not appear until much higher exposures (7000 ppm) from drinking water (546 mg/kg) assuming water consumption was not reduced which is unlikely. However, this report did not include details of protocol and results.

In addition, factors which may influence absorption rate from the GI tract are completely characterized and an estimated RfD should be designed to be protective across a wide range of exposure scenarios.

Consideration of all of these factors suggests that the LOAEL of 50 mg/kg from the Dow (1945) study should be appropriate to derive an RfD for phenol. This is below the level which could be estimated using the LOAEL of 120 mg/kg for fetotoxicity as evidenced by significant but slight decreases in body weight with an uncertainty factor of 1000. The LOAEL of 50 mg/kg (Dow Chemical Company, 1945) administered 5 days/week could be expanded to 35.7 mg/kg/day on a 7-day basis. By applying an uncertainty factor of 1000 (10 for intraspecies sensitivity, 10 for interspecies extrapolation and 10 to expand subchronic to chronic exposure) to this LOAEL an RfD of 0.04 mg/kg/day or 2.5 mg/day for a 70 kg man can be derived.

## 9. REPORTABLE QUANTITIES RANKING (RQ)

### 9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Details of the chronic and subchronic oral and inhalation studies on the toxic effects of phenol were discussed in Section 5.5. and summarized in Tables 5-4 and 5-5. In addition, two teratogenicity studies (see Section 5.3.) are available for consideration for the derivation of the RQ.

In an epidemiologic study, humans exposed to phenol in the drinking water at >0.1 mg/ℓ for ~7 months following an accidental spill had significantly increased incidences of burning mouth, mouth sores and diarrhea than did persons whose drinking water supply contained ≤0.1 mg phenol/ℓ (Baker et al, 1978). This study is unsuitable for derivation of the RQ because an MED cannot be defined.

In a multigeneration study, rats were administered drinking water containing phenol at 100-12,000 ppm for up to 5 generations (Heller and Pursell, 1938). No effects on reproduction were observed at ≤5000 ppm but at 7000 ppm, offspring had retarded growth; at 8000 ppm dams failed to care for the pups, and at ≥10000 ppm, reproduction was inhibited; offspring died at birth and adults died early. In a previous determination of the RQ for phenol (U.S. EPA, 1983), this study was considered to be unsuitable for the derivation of the RQ because the doses equivalent to 5000 ppm (≥390 mg/kg/day, assuming a rat imbibes an amount of water equal to 7.8% of its body weight) are near or in excess of the single-dose oral $LD_{50}$ in rats of 435 mg/kg for phenol (U.S. EPA, 1980), making the study difficult to interpret. In an NCI (1980) bioassay, however, rats were administered phenol in drinking water at ≤10,000 ppm (780 mg/kg/day) for 90 days without adverse effects. The discrepancies may be due to the fact that in the $LD_{50}$ determinations, phenol was administered as a bolus, whereas in the drinking water

studies exposure was intermittent and over the course of a day. Therefore, the study of Heller and Pursell (1938) may be suitable for the derivation of the RQ.

In an 12-month study in which rats were exposed to phenol in the drinking water at 0, 800, 1200, 1600, 2000 or 2400 ppm, the only effect was reduced body weight at 2000 and 2400 ppm (Deichmann and Oesper, 1940). Based on actual water consumption data, the exposures in this study were equivalent to 0, 21, 30, 49, 56 and 55 mg/rat/day, respectively, indicating that water consumption was also decreased at the high exposure levels. Since the reduced body weight may have been secondary to reduced water intake, this study is unsuitable for the derivation of the RQ.

Decreased body weight and reduced water intake were also observed in rats and mice exposed at drinking water concentrations of 10,000 ppm for 90 days and 2500 and 500 ppm for 103 weeks (NCI, 1980). In addition, male and female rats exposed at 5000 ppm for 103 weeks and observed for 2 additional weeks had increased incidences of chronic kidney inflammation. The NCI (1980) carcinogenicity study was not considered for RQ derivation in the previous determination (U.S. EPA, 1983) because no significant increased incidences of non-neoplastic changes were reported by NCI (1980). On closer analysis of the tabulated non-neoplastic lesions, however, increased incidences of the kidney lesion were noted, and statistical analysis using Fisher's Exact Test indicated that the incidences were significantly ($p \leq 0.0019$ for males and $p \leq 0.00001$ for females) increased compared with control. The 5000 ppm exposure level is equivalent to 344 mg/kg/day, calculated by multiplying 5000 ppm by 103/105 weeks, by the assumed fraction of the body weight consumed daily as water (7.8%) and by the percentage of decreased water consumption compared with controls (90%).

Slight kidney changes were also observed in a 6-month study in which rats were treated by gavage at 50 mg/kg/day, 5 days/week (TWA=37.5 mg/kg/day) (Dow Chemical Company, 1976). At 100 mg/kg/day, 5 days/week (TWA=71.4 mg/kg/day), moderate kidney and slight liver changes were observed. Similar effects were observed in rabbits treated with phenol at 100 mg/kg/day for 20 days.

In one teratogenicity study (Jones-Price et al., 1983a), phenol was not teratogenic to the offspring of rats at gavage doses $\leq$120 mg/kg/day, but mean fetal body weight per litter was significantly decreased at 120 mg/kg/day compared with controls. No maternal toxicity was observed at these doses.

In the second teratogenicity study (Jones-Price et al., 1983b), phenol administered to pregnant mice by gavage resulted in growth retardation, decreased prenatal viability, abnormal structural development and an increased incidence of cleft palate at $\geq$200 mg/kg/day. These doses were also toxic to dams, resulting in tremors, weight loss and death.

In inhalation experiments, no adverse effects were observed in mice, rats or monkey at 5 ppm (19 mg/m$^3$), 8 hours/day, 5 days/week for 90 days (Sandage, 1961). Inhalation exposure of 100-200 mg/m$^3$, 7 hours/day, 5 days/week resulted in hypoactivity, weight loss, respiratory difficulties, hind leg paralysis and death in guinea pigs (29 exposures), histopathologic changes in the myocardium, lungs, liver and kidneys of guinea pigs (29 exposures) and rabbits (63 exposures), but no effects in rats (Deichmann et al., 1944).

The data used to calculate CSs are presented in Table 9-1. The chronic human MED is calculated from the oral animal dose by using the cube root of

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TABLE 9-1

Composite Scores for Phenol

| Species/ Strain | Route | Dose/Exposure | Chronic Human MED (mg/day) | $RV_d$ | Effects | $RV_e$ | CS | RQ | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Mouse/CD-1 | oral (gavage) | 200 mg/kg/day, gestational days 6-15 | 1056 | 1 | Increased incidence of cleft palate, abnormal structural development, prenatal death at doses toxic to dams | 9 | 9 | 1000 | Jones-Price et al., 1983b |
| Rats/CD | oral (gavage) | 120 mg/kg/day gestational days 6-15 | 1436 | 1 | Increased proportion of litters with resorption sites, decreased fetal body weight with no evidence of maternal toxicity | 8 | 8 | 1000 | Jones-Price et al., 1983a |
| Rats/CD | oral in drinking water | 8000 ppm (624 mg/kg/day), several generations | 7469 | 1 | Dams were irritable and failed to care for offspring | 8 | 8 | 1000 | Heller and Pursell, 1938 |
| Rats/CD | oral in drinking water | 10,000 ppm (780 mg/kg/day), several generations | 9336 | 1 | Reproduction inhibited, adults died early, offspring died at birth | 10 | 10 | 1000 | Heller and Pursell, 1938 |
| Rats/F344 | oral (in drinking water) | 344 mg/kg/day/ 103 weeks | 4118 mg/day | 1 | Chronic kidney inflammation | 4 | 4 | 5000 | NCI, 1980 |
| Rats | oral (gavage) | 50 mg/kg/day 5 days/week for 6 months | 42.7* | 3.1 | Slight kidney damage | 4 | 12.4 | 1000 | Dow Chemical Co., 1976 |
| Rats | oral (gavage) | 100 mg/kg/day 5 days/week for 6 months | 85.5* | 2.6 | Liver and kidney damage | 5 | 13 | 1000 | Dow Chemical Co., 1976 |
| Guinea pigs | inhalation | 100 mg/m³ 7 hours/day, 5 days/week 29 exposures | 5.6 mg/day* | 4.4 | Death in 5/12 exposed animals by 20th exposure, external and internal signs of toxicity | 10 | 44 | 10 | Deichmann et al., 1944 |

*An uncertainty factor of 10 was used to estimate chronic exposure.

UF = Uncertainty factor



06/27/85

the body weight ratio for interspecies conversion and assuming weights of 0.35 kg for rats 0.03 kg for mice and 70 kg for humans. Animal doses from subchronic studies are divided by an uncertainty factor of 10 to take into account the subchronic nature of the data. As can be seen from Table 9-1, the $RV_d$s associated with the human MEDs calculated from oral doses range from ~1-3 and the corresponding $RV_e$s for the various effects reported range from 4-8, yielding CSs ($RV_d$x$RV_e$) for the oral studies that range from 4-13.6.

From the data on inhalation exposure reported by Deichmann et al. (1944), it is obvious that guinea pigs are more susceptible to the toxic effects of inhaled phenol than are rabbits or rats. In this subchronic study animals were exposed to 100-200 mg phenol/$m^3$, 7 hours/day, 5 days/week. Five of 12 guinea pigs died by the 28th day of exposure, an effect that corresponds to an $RV_e$ of 10. A chronic human MED of 5.6 mg/day can be calculated from the exposure level of 100 mg/$m^3$ by expanding the exposure from 7-24 hours and from 5-7 days for continuous exposure, and by applying a guinea pig 24-hour ventilatory volume of 0.09 $m^3$/day assuming guinea pigs weigh 0.43 kg and multiplying by the cube root of the body weight ratio. A safety factor of 10 was applied to convert from subchronic to chronic exposure. This MED corresponds to an $RV_d$ of 4.4. A CS of 44 is obtained, which corresponds to an RQ of 10. An exposure period of 29 days, as used in this study, would normally be insufficient for the derivation of an RQ; however, the early deaths observed with this species indicate that data from the longer exposures of other species may not provide sufficient protection. The RQ reported in Table 9-2 is derived from the same data as the RQ reported in U.S. EPA (1983).

TABLE 9-2

Phenol

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

| | |
|---|---|
| Route: | inhalation |
| Dose*: | 5.6 mg/day |
| Effect: | death in guinea pigs |
| Reference: | Deichmann et al., 1944 |
| $RV_d$: | 4.4 |
| $RV_e$: | 10 |
| Composite Score: | 44 |
| RQ: | 10 |

*Equivalent human dose

## 9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The carcinogenicity data available for phenol were discussed in Section 5.1. and Table 5-1. Phenol was administered in the drinking water of rats and mice at 2500 and 5000 ppm for 2 years (NCI, 1980). Statistically significant increased incidences of pheochromocytomas of the adrenal medulla and leukemias or lymphomas were observed in male rats at 2500 ppm, but not at 5000 ppm. No increased incidences of tumors were observed in female rats or male and female mice. NCI (1980) concluded that phenol was not carcinogenic under the conditions of the study; however, it was suggested that phenol be considered for retesting. Phenol has been reported to be a weak carcinogen upon dermal application to mice (Boutwell and Bosch, 1959) and also to be a tumor promoter (Boutwell and Bosch, 1959; Salaman and Glendenning, 1957) but not a cocarcinogen (Van Duuren and Goldschmidt, 1976; Van Duuren et al., 1971, 1973). Although these studies indicate that phenol has an effect on the etiology of cancer development, the data is inadequate to evaluate the "complete" carcinogenic potential. Using the EPA criteria for evaluating the overall weight of evidence of carcinogenicity to humans, phenol is most appropriately classified as a Group D chemical, indicating that there is inadequate evidence for assessment of carcinogenicity in humans. Given a Group D classification, it follows that there is no basis for derivation of cancer potency factors.

PHENOL

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## APPENDIX

## LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in July, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:


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In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:


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